

TARGETED CHROMOSOMAL GENOMIC ALTERATIONS WITH MODIFIED SINGLE STRANDED OLIGONUCLEOTIDES

Field Of The Invention

The technical field of the invention is oligonucleotide-directed repair or alteration of genetic information using novel chemically modified oligonucleotides. Such genetic information is preferably from a eukaryotic organism, i.e. a plant, animal or fungus.

Background Of The Invention

A number of methods have been developed specifically to alter the sequence of an isolated DNA in addition to methods to alter directly the genomic information of various plants, fungi and animals, including humans ("gene therapy"). The latter methods generally include the use of viral or plasmid vectors carrying nucleic acid sequences encoding partial or complete portions of a particular protein which is expressed in a cell or tissue to effect the alteration. The expression of the particular protein then results in the desired phenotype. For example, retroviral vectors containing a transgenic DNA sequence allowing for the production of a normal CFTR protein when administered to defective cells are described in U.S. Patent 5,240,846. Others have developed different "gene therapy vectors" which include, for example, portions of adenovirus (Ad) or adeno-associated virus (AAV), or other viruses. The virus portions used are often long terminal repeat sequences which are added to the ends of a transgene of choice along with other necessary control sequences which allow expression of the transgene. See U.S. Patents 5,700,470 and 5,139,941. Similar methods have been developed for use in plants. See, for example, U.S. Patent 4,459,355 which describes a method for transforming plants with a DNA vector and U.S. Patent 5,188,642 which describes cloning or expression vectors containing a transgenic DNA sequence which when expressed in plants confers resistance to the herbicide glyphosate. The use of such transgene vectors in any eukaryotic organism adds one or more exogenous copies of a gene, which gene may be foreign to the host, in a usually random fashion at one or more integration sites of the organism's genome at some frequency. The gene which was originally present in the genome, which may be a normal allelic variant, mutated, defective, and/or functional, is retained in the genome of the host.

These methods of gene correction are problematic in that complications which can compromise the health of the recipient, or even lead to death, may result. One such problem is that insertion of exogenous nucleic acid at random location(s) in the genome can have deleterious effects. Another problem with such systems includes the addition of unnecessary and unwanted genetic material to the genome of the recipient, including, for example, viral or other vector remnants, control sequences required to allow production of the transgene protein, and reporter genes or resistance markers. Such remnants and added sequences may have presently unrecognized consequences, for example, involving genetic rearrangements of the recipient genomes. Other problems associated with these types of traditional gene therapy methods include autoimmune suppression of cells expressing an inserted gene due to the presence of foreign antigens. Concerns have also been raised with consumption, especially by humans, of plants containing exogenous genetic material.

More recently, simpler systems involving poly- or oligo- nucleotides have been described for use in the alteration of genomic DNA. These chimeric RNA-DNA oligonucleotides, requiring contiguous RNA and DNA bases in a double-stranded molecule folded by complementarity into a double hairpin conformation, have been shown to effect single basepair or frameshift alterations, for example, for mutation or repair of plant or animal genomes. See, for example, WO 99/07865 and U.S. Patent 5,565,350. In the chimeric RNA-DNA oligonucleotide, an uninterrupted stretch of DNA bases within the molecule is required for sequence alteration of the targeted genome while the obligate RNA residues are involved in complex stability. Due to the length, backbone composition, and structural configuration of these chimeric RNA-DNA molecules, they are expensive to synthesize and difficult to purify. Moreover, if the RNA-containing strand of the chimeric RNA-DNA oligonucleotide is designed so as to direct gene conversion, a series of mutagenic reactions resulting in nonspecific base alteration can result. Such a result compromises the utility of such a molecule in methods designed to alter the genomes of plants and animals, including in human gene therapy applications.

Alternatively, other oligo- or poly- nucleotides have been used which require a triplex forming, usually polypurine or polypyrimidine, structural domain which binds to a DNA helical duplex through Hoogsteen interactions between the major groove of the DNA duplex and the oligonucleotide. Such oligonucleotides may have an additional DNA reactive moiety, such as psoralen, covalently linked to the oligonucleotide. These reactive moieties function as effective intercalation agents, stabilize the formation of a triplex and can be mutagenic. Such agents may be required in order to stabilize the triplex forming domain of the oligonucleotide with the DNA double helix if the Hoogsteen interactions from the oligonucleotide/target base composition are insufficient. See, e.g., U.S. Patent 5,422,251. The utility of

these oligonucleotides for directing gene conversion is compromised by a high frequency of nonspecific base changes.

In more recent work, the domain for altering a genome is linked or tethered to the triplex forming domain of the bi-functional oligonucleotide, adding an additional linking or tethering functional domain to the oligonucleotide. See, e.g., Culver et al., Nature Biotechnology 17: 989-93 (1999). Such chimeric or triplex forming molecules have distinct structural requirements for each of the different domains of the complete poly- or oligo-nucleotide in order to effect the desired genomic alteration in either episomal or chromosomal targets.

Other genes, e.g. CFTR, have been targeted by homologous recombination using duplex fragments having several hundred basepairs. See, e.g., Kunzelmann et al., Gene Ther. 3:859-867 (1996). Early experiments to mutagenize an antibiotic resistance indicator gene by homologous recombination used an unmodified DNA oligonucleotide with no functional domains other than a region of complementary sequence to the target. See Campbell et al., New Biologist 1: 223-227 (1989). These experiments required large concentrations of the oligonucleotide, exhibited a very low frequency of episomal modification of a targeted exogenous plasmid gene not normally found in the cell and have not been reproduced. However, as shown in the examples herein, we have observed that an unmodified DNA oligonucleotide can convert a base at low frequency which is detectable using the assay systems described herein.

Artificial chromosomes can be useful for the screening purposed identified herein. These molecules are man-made linear or circular DNA molecules constructed from essential cis-acting DNA sequence elements that are responsible for the proper replication and partitioning of natural chromosomes (Murray et al., 1983). The essential elements are: (1) Autonomous Replication Sequences (ARS), (2) Centromeres, and (3) Telomeres.

Yeast artificial chromosomes (YACs) allow large genomic DNA to be modified and used for generating transgenic animals [Burke et al., Science 236:806; Peterson et al., Trends Genet. 13:61 (1997); Choi, et al., Nat. Genet., 4:117-223 (1993), Davies, et al., Biotechnology 11:911-914 (1993), Matsuura, et al., Hum. Mol. Genet., 5:451-459 (1996), Peterson et al., Proc. Natl. Acad. Sci., 93:6605-6609 (1996); and Schedl, et al., Cell, 86:71-82 (1996)]. Other vectors also have been developed for the cloning of large segments of mammalian DNA, including cosmids, and bacteriophage P1 [Sternberg et al., Proc. Natl. Acad. Sci. U.S.A., 87:103-107 (1990)]. YACs have certain advantages over these alternative large capacity cloning vectors [Burke et al., Science, 236:806-812 (1987)]. The

maximum insert size is 35-30 kb for cosmids, and 100 kb for bacteriophage P1, both of which are much smaller than the maximal insert for a YAC.

An alternative to YACs are E. coli based cloning systems based on the E. coli fertility factor that have been developed to construct large genomic DNA insert libraries. They are bacterial artificial chromosomes (BACs) and P-1 derived artificial chromosomes (PACs) [Mejia et al., Genome Res. 7:179-186 (1997); Shizuya et al., Proc. Natl. Acad. Sci. 89:8794-8797 (1992); Ioannou et al., Nat. Genet., 6:84-89 (1994); Hosoda et al., Nucleic Acids Res. 18:3863 (1990)]. BACs are based on the E. coli fertility plasmid (F factor); and PACs are based on the bacteriophage P1. These vectors propagate at a very low copy number (1-2 per cell) enabling genomic inserts up to 300 kb in size to be stably maintained in recombination deficient hosts. Furthermore, the PACs and BACs are circular DNA molecules that are readily isolated from the host genomic background by classical alkaline lysis [Birnboim et al., Nucleic Acids Res. 7:1513-1523 (1979)].

Oligonucleotides designed for use in the alteration of genetic information are significantly different from oligonucleotides designed for antisense approaches. For example, antisense oligonucleotides are perfectly complementary to and bind an mRNA strand in order to modify expression of a targeted mRNA and are used at high concentration. As a consequence, they are unable to produce a gene conversion event by either mutagenesis or repair of a defect in the chromosomal DNA of a host genome. Furthermore, the backbone chemical composition used in most oligonucleotides designed for use in antisense approaches renders them inactive as substrates for homologous pairing or mismatch repair enzymes and the high concentrations of oligonucleotide required for antisense applications can be toxic with some types of nucleotide modifications. In addition, antisense oligonucleotides must be complementary to the mRNA and therefore, may not be complementary to the other DNA strand or to genomic sequences that span the junction between intron sequence and exon sequence.

A need exists for simple, inexpensive oligonucleotides capable of producing targeted alteration of genetic material such as those described herein as well as methods to identify optimal oligonucleotides that accurately and efficiently alter target DNA.

Summary Of The Invention

Novel, modified single-stranded nucleic acid molecules that direct gene alteration in plants, fungi and animals are identified and the efficiency of alteration is analyzed both in vitro using a cell-free extract assay and in vivo using a yeast cell system. The alteration in an oligonucleotide of the invention may comprise an insertion, deletion, substitution, as well as any combination of these. Site

specific alteration of DNA is not only useful for studying function of proteins in vivo, but it is also useful for creating animal models for human disease, and in gene therapy. As described herein, oligonucleotides of the invention target directed specific gene alterations in genomic double-stranded DNA cells. The target DNA can be normal, cellular chromosomal DNA, extrachromosomal DNA present in cells in different forms including, e.g., mammalian artificial chromosomes (MACs), PACs from P-1 vectors, yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), plant artificial chromosomes (PLACs), as well as episomal DNA, including episomal DNA from an exogenous source such as a plasmid or recombinant vector. Many of these artificial chromosome constructs containing human DNA can be obtained from a variety of sources, including, e.g., the Whitehead Institute, and are described, e.g., in Cohen et al., Nature 336:698-701 (1993) and Chumakov, et al., Nature 377:174-297 (1995). The target DNA may be transcriptionally silent or active. In a preferred embodiment, the target DNA to be altered is the non-transcribed strand of a genomic DNA duplex.

The low efficiency of gene alteration obtained using unmodified DNA oligonucleotides is believed to be largely the result of degradation by nucleases present in the reaction mixture or the target cell. Although different modifications are known to have different effects on the nuclease resistance of oligonucleotides or stability of duplexes formed by such oligonucleotides (see, e.g., Koshkin et al., J. Am. Chem. Soc., 120:13252-3), we have found that it is not possible to predict which of any particular known modification would be most useful for any given alteration event, including for the construction of gene conversion oligonucleotides, because of the interaction of different as yet unidentified proteins during the gene alteration event. Herein, a variety of nucleic acid analogs have been developed that increase the nuclease resistance of oligonucleotides that contain them, including, e.g., nucleotides containing phosphorothioate linkages or 2'-O-methyl analogs. We recently discovered that single-stranded DNA oligonucleotides modified to contain 2'-O-methyl RNA nucleotides or phosphorothioate linkages can enable specific alteration of genetic information at a higher level than either unmodified single-stranded DNA or a chimeric RNA/DNA molecule. See priority applications incorporated herein in their entirety; see also Gamper et al., Nucleic Acids Research 28: 4332-4339 (2000). We also found that additional nucleic acid analogs which increase the nuclease resistance of oligonucleotides that contain them, including, e.g., "locked nucleic acids" or "LNAs", xylo-LNAs and L-ribo-LNAs; see, for example, Wengel & Nielsen, WO 99/14226; Wengel, WO 00/56748 and Wengel, WO 00/66604; also allow specific targeted alteration of genetic information.

The assay allows for determining the optimum length of the oligonucleotide, optimum sequence of the oligonucleotide, optimum position of the mismatched base or bases, optimum chemical

modification or modifications, optimum strand targeted for identifying and selecting the most efficient oligonucleotide for a particular gene alteration event by comparing to a control oligonucleotide. Control oligonucleotides may include a chimeric RNA-DNA double hairpin oligonucleotide directing the same gene alteration event, an oligonucleotide that matches its target completely, an oligonucleotide in which all linkages are phosphorothiolated, an oligonucleotide fully substituted with 2'-O-methyl analogs or an RNA oligonucleotide. Such control oligonucleotides either fail to direct a targeted alteration or do so at a lower efficiency as compared to the oligonucleotides of the invention. The assay further allows for determining the optimum position of a gene alteration event within an oligonucleotide, optimum concentration of the selected oligonucleotide for maximum alteration efficiency by systematically testing a range of concentrations, as well as optimization of either the source of cell extract by testing different organisms or strains, or testing cells derived from different organisms or strains, or cell lines. Using a series of single-stranded oligonucleotides, comprising all RNA or DNA residues and various mixtures of the two, several new structures are identified as viable molecules in nucleotide conversion to direct or repair a genomic mutagenic event. When extracts from mammalian, plant and fungal cells are used and are analyzed using a genetic readout assay in bacteria, single-stranded oligonucleotides having one of several modifications are found to be more active than a control RNA-DNA double hairpin chimera structure when evaluated using an *in vitro* gene repair assay. Similar results are also observed *in vivo* using yeast, mammalian, rodent, monkey, human and embryonic cells, including stem cells. Molecules containing various lengths of modified bases were found to possess greater activity than unmodified single-stranded DNA molecules.

Detailed Description Of The Invention

The present invention provides oligonucleotides having chemically modified, nuclease resistant residues, preferably at or near the termini of the oligonucleotides, and methods for their identification and use in targeted alteration of genetic material, including gene mutation, targeted gene repair and gene knockout. The oligonucleotides are preferably used for mismatch repair or alteration by changing at least one nucleic acid base, or for frameshift repair or alteration by addition or deletion of at least one nucleic acid base. The oligonucleotides of the invention direct any such alteration, including gene correction, gene repair or gene mutation and can be used, for example, to introduce a polymorphism or haplotype or to eliminate ("knockout") a particular protein activity.

The oligonucleotides of the invention are designed as substrates for homologous pairing and repair enzymes and as such have a unique backbone composition that differs from chimeric RNA-

DNA double hairpin oligonucleotides, antisense oligonucleotides, and/or other poly- or oligo-nucleotides used for altering genomic DNA, such as triplex forming oligonucleotides. The single-stranded oligo-nucleotides described herein are inexpensive to synthesize and easy to purify. In side-by-side comparisons, an optimized single-stranded oligonucleotide comprising modified residues as described herein is significantly more efficient than a chimeric RNA-DNA double hairpin oligonucleotide in directing a base substitution or frameshift mutation in a cell-free extract assay.

We have discovered that single-stranded oligonucleotides having a DNA domain surrounding the targeted base, with the domain preferably central to the poly- or oligo-nucleotide, and having at least one modified end, preferably at the 3' terminal region are able to alter a target genetic sequence and with an efficiency that is higher than chimeric RNA-DNA double hairpin oligonucleotides disclosed in US Patent 5,565,350. Oligonucleotides of the invention can efficiently be used to introduce targeted alterations in a genetic sequence of DNA in the presence of human, animal, plant, fungal (including yeast) proteins and in cultured cells of human liver, lung, colon, cervix, kidney, epithelium and cancer cells and in monkey, hamster, rat and mouse cells of different types, as well as embryonic stem cells. Cells for use in the invention include, e.g., fungi including *S. cerevisiae*, *Ustilago maydis* and *Candida albicans*, mammalian, mouse, hamster, rat, monkey, human and embryonic cells including stem cells. The DNA domain is preferably fully complementary to one strand of the gene target, except for the mismatch base or bases responsible for the gene alteration or conversion events. On either side of the preferably central DNA domain, the contiguous bases may be either RNA bases or, preferably, are primarily DNA bases. The central DNA domain is generally at least 8 nucleotides in length. The base(s) targeted for alteration in the most preferred embodiments are at least about 8, 9 or 10 bases from one end of the oligonucleotide.

According to certain embodiments, the termini of the oligonucleotides of the present invention comprise phosphorothioate modifications, LNA backbone modifications, or 2'-O-methyl base analogs, or any combination of these modifications. Oligonucleotides comprising 2'-O-methyl or LNA analogs are a mixed DNA/RNA polymer. These oligonucleotides are, however, single-stranded and are not designed to form a stable internal duplex structure within the oligonucleotide. The efficiency of gene alteration is surprisingly increased with oligonucleotides having internal complementary sequence comprising phosphorothioate modified bases as compared to 2'-O-methyl modifications. This result indicates that specific chemical interactions are involved between the converting oligonucleotide and the proteins involved in the conversion. The effect of other such chemical interactions to produce nuclease resistant termini using modifications other than LNA, phosphorothioate linkages, or 2'-O-methyl analog

incorporation into an oligonucleotide can not yet be predicted because the proteins involved in the alteration process and their particular chemical interaction with the oligonucleotide substituents are not yet known and cannot be predicted.

In the examples, correcting oligonucleotides of defined sequence are provided for
5 correction of genes mutated in human diseases. In the tables of these examples, the oligonucleotides of the invention are not limited to the particular sequences disclosed. The oligonucleotides of the invention include extensions of the appropriate sequence of the longer 120 base oligonucleotides which can be added base by base to the smallest disclosed oligonucleotides of 17 bases. Thus the oligonucleotides of the invention include for each correcting change, oligonucleotides of length 18, 19, 20, 21, 22, 23, 24, 25,
10 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, or 120 with further single-nucleotide additions up to the longest sequence disclosed. Moreover, the oligonucleotides of the invention do not require a symmetrical extension on either side of the central DNA domain. Similarly, the oligonucleotides of the invention as disclosed in the various tables for correction of human diseases contain phosphorothioate linkages, 2'-O-methyl analogs or LNAs or any combination of these modifications just as the assay oligonucleotides do.

The present invention, however, is not limited to oligonucleotides that contain any
20 particular nuclease resistant modification. Oligonucleotides of the invention may be altered with any combination of additional LNAs, phosphorothioate linkages or 2'-O-methyl analogs to maximize conversion efficiency. For oligonucleotides of the invention that are longer than about 17 to about 25 bases in length, internal as well as terminal region segments of the backbone may be altered. Alternatively, simple fold-back structures at each end of a oligonucleotide or appended end groups may
25 be used in addition to a modified backbone for conferring additional nuclease resistance.

The different oligonucleotides of the present invention preferably contain more than one of the aforementioned backbone modifications at each end. In some embodiments, the backbone modifications are adjacent to one another. However, the optimal number and placement of backbone modifications for any individual oligonucleotide will vary with the length of the oligonucleotide and the
30 particular type of backbone modification(s) that are used. If constructs of identical sequence having phosphorothioate linkages are compared, 2, 3, 4, 5, or 6 phosphorothioate linkages at each end are preferred. If constructs of identical sequence having 2'-O-methyl base analogs are compared, 1, 2, 3 or 4

analogs are preferred. The optimal number and type of backbone modifications for any particular oligonucleotide useful for altering target DNA may be determined empirically by comparing the alteration efficiency of the oligonucleotide comprising any combination of the modifications to a control molecule of comparable sequence using any of the assays described herein. The optimal position(s) for oligonucleotide modifications for a maximally efficient altering oligonucleotide can be determined by testing the various modifications as compared to control molecule of comparable sequence in one of the assays disclosed herein. In such assays, a control molecule includes, e.g., a completely 2'-O-methyl substituted molecule, a completely complementary oligonucleotide, or a chimeric RNA-DNA double hairpin.

Increasing the number of phosphorothioate linkages, LNAs or 2'-O-methyl bases beyond the preferred number generally decreases the gene repair activity of a 25 nucleotide long oligonucleotide. Based on analysis of the concentration of oligonucleotide present in the extract after different time periods of incubation, it is believed that the terminal modifications impart nuclease resistance to the oligonucleotide thereby allowing it to survive within the cellular environment. However, this may not be the only possible mechanism by which such modifications confer greater efficiency of conversion. For example, as disclosed herein, certain modifications to oligonucleotides confer a greater improvement to the efficiency of conversion than other modifications.

Efficiency of conversion is defined herein as the percentage of recovered substrate molecules that have undergone a conversion event. Depending on the nature of the target genetic material, e.g. the genome of a cell, efficiency could be represented as the proportion of cells or clones containing an extrachromosomal element that exhibit a particular phenotype. Alternatively, representative samples of the target genetic material can be sequenced to determine the percentage that have acquired the desired change. The oligonucleotides of the invention in different embodiments can alter DNA one, two, three, four, five, six, seven, eight, nine, ten, twelve, fifteen, twenty, thirty, and fifty or more fold more than control oligonucleotides. Such control oligonucleotides are oligonucleotides with fully phosphorothiolated linkages, oligonucleotides that are fully substituted with 2'-O-methyl analogs, a perfectly matched oligonucleotide that is fully complementary to a target sequence or a chimeric DNA-RNA double hairpin oligonucleotide such as disclosed in US Patent 5,565,350.

In addition, for a given oligonucleotide length, additional modifications interfere with the ability of the oligonucleotide to act in concert with the cellular recombination or repair enzyme machinery which is necessary and required to mediate a targeted substitution, addition or deletion event in DNA. For

example, fully phosphorothiolated or fully 2-O-methylated molecules are inefficient in targeted gene alteration.

5 The oligonucleotides of the invention as optimized for the purpose of targeted alteration of genetic material, including gene knockout or repair, are different in structure from antisense oligonucleotides that may possess a similar mixed chemical composition backbone. The oligonucleotides of the invention differ from such antisense oligonucleotides in chemical composition, structure, sequence, and in their ability to alter genomic DNA. Significantly, antisense oligonucleotides fail to direct targeted gene alteration. The oligonucleotides of the invention may target either the Watson or the Crick strand of DNA and can include any component of the genome including, for example, intron and exon sequences. 10 The preferred embodiment of the invention is a modified oligonucleotide that binds to the non-transcribed strand of a genomic DNA duplex. In other words, the preferred oligonucleotides of the invention target the sense strand of the DNA, i.e. the oligonucleotides of the invention are complementary to the non-transcribed strand of the target duplex DNA. The sequence of the non-transcribed strand of a DNA duplex is found in the mRNA produced from that duplex, given that mRNA uses uracil-containing nucleotides in place of thymine-containing nucleotides. 15

Moreover, the initial observation that single-stranded oligonucleotides comprising these modifications and lacking any particular triplex forming domain have reproducibly enhanced gene repair activity in a variety of assay systems as compared to a chimeric RNA-DNA double-stranded hairpin control or single-stranded oligonucleotides comprising other backbone modifications was surprising. The single-stranded molecules of the invention totally lack the complementary RNA binding structure that stabilizes a normal chimeric double-stranded hairpin of the type disclosed in U.S. Patent 5,565,350 yet is more effective in producing targeted base conversion as compared to such a chimeric RNA-DNA double-stranded hairpin. In addition, the molecules of the invention lack any particular triplex forming domain involved in Hoogsteen interactions with the DNA double helix and required by other known oligonucleotides in other oligonucleotide dependant gene conversion systems. Although the lack of these functional domains was expected to decrease the efficiency of an alteration in a sequence, just the opposite occurs: the efficiency of sequence alteration using the modified oligonucleotides of the invention is higher than the efficiency of sequence alteration using a chimeric RNA-DNA hairpin targeting the same sequence alteration. Moreover, the efficiency of sequence alteration or gene conversion directed by an unmodified oligonucleotide is many times lower as compared to a control chimeric RNA-DNA molecule or the modified oligonucleotides of the invention targeting the same sequence alteration. Similarly, 25 30

molecules containing at least 3 2'-O-methyl base analogs are about four to five fold less efficient as compared to an oligonucleotide having the same number of phosphorothioate linkages.

The oligonucleotides of the present invention for alteration of a single base are about 17 to about 121 nucleotides in length, preferably about 17 to about 74 nucleotides in length. Most preferably, however, the oligonucleotides of the present invention are at least about 25 bases in length, unless there are self-dimerization structures within the oligonucleotide. If the oligonucleotide has such an unfavorable structure, lengths longer than 35 bases are preferred. Oligonucleotides with modified ends both shorter and longer than certain of the exemplified, modified oligonucleotides herein function as gene repair or gene knockout agents and are within the scope of the present invention.

Once an oligomer is chosen, it can be tested for its tendency to self-dimerize, since self-dimerization may result in reduced efficiency of alteration of genetic information. Checking for self-dimerization tendency can be accomplished manually or, more preferably, by using a software program. One such program is Oligo Analyzer 2.0, available through Integrated DNA Technologies (Coralville, IA 52241) (<http://www.idtdna.com>); this program is available for use on the world wide web at

[http://www.idtdna.com/program/oligoanalyzer/
oligoanalyzer.asp](http://www.idtdna.com/program/oligoanalyzer/oligoanalyzer.asp).

For each oligonucleotide sequence input into the program, Oligo Analyzer 2.0 reports possible self-dimerized duplex forms, which are usually only partially duplexed, along with the free energy change associated with such self-dimerization. Delta G-values that are negative and large in magnitude, indicating strong self-dimerization potential, are automatically flagged by the software as "bad". Another software program that analyzes oligomers for pair dimer formation is Primer Select from DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715, Phone: (608) 258-7420 (<http://www.dnastar.com/products/PrimerSelect.html>).

If the sequence is subject to significant self-dimerization, the addition of further sequence flanking the "repair" nucleotide can improve gene correction frequency.

Generally, the oligonucleotides of the present invention are identical in sequence to one strand of the target DNA, which can be either strand of the target DNA, with the exception of one or more targeted bases positioned within the DNA domain of the oligonucleotide, and preferably toward the middle between the modified terminal regions. Preferably, the difference in sequence of the oligonucleotide as compared to the targeted genomic DNA is located at about the middle of the oligonucleotide sequence. In a preferred embodiment, the oligonucleotides of the invention are complementary to the non-transcribed strand of a duplex. In other words, the preferred oligonucleotides target the sense strand of the DNA, i.e.

the oligonucleotides of the invention are preferably complementary to the strand of the target DNA the sequence of which is found in the mRNA.

5 The oligonucleotides of the invention can include more than a single base change. In an oligonucleotide that is about a 70-mer, with at least one modified residue incorporated on the ends, as disclosed herein, multiple bases can be simultaneously targeted for change. The target bases may be up to 27 nucleotides apart and may not be changed together in all resultant plasmids in all cases. There is a frequency distribution such that the closer the target bases are to each other in the central DNA domain within the oligonucleotides of the invention, the higher the frequency of change in a given cell. Target bases only two nucleotides apart are changed together in every case that has been analyzed. The farther apart the two target bases are, the less frequent the simultaneous change. Thus, oligonucleotides of the invention may be used to repair or alter multiple bases rather than just one single base. For example, in a 74-mer oligonucleotide having a central base targeted for change, a base change event up to about 27 nucleotides away can also be effected. The positions of the altering bases within the oligonucleotide can be optimized using any one of the assays described herein. Preferably, the altering bases are at least about 8 nucleotides from one end of the oligonucleotide.

10 The oligonucleotides of the present invention can be introduced into cells by any suitable means. According to certain preferred embodiments, the modified oligonucleotides may be used alone. Suitable means, however, include the use of polycations, cationic lipids, liposomes, polyethylenimine (PEI), electroporation, biolistics, microinjection and other methods known in the art to facilitate cellular uptake. According to certain preferred embodiments of the present invention, the isolated cells are treated in culture according to the methods of the invention, to mutate or repair a target gene. Modified cells may then be reintroduced into the organism as, for example, in bone marrow having a targeted gene. Alternatively, modified cells may be used to regenerate the whole organism as, for example, in a plant having a desired targeted genomic change. In other instances, targeted genomic alteration, including repair or mutagenesis, may take place in vivo following direct administration of the modified, single-stranded oligonucleotides of the invention to a subject.

25 The single-stranded, modified oligonucleotides of the present invention have numerous applications as gene repair, gene modification, or gene knockout agents. Such oligonucleotides may be advantageously used, for example, to introduce or correct multiple point mutations. Each mutation leads to the addition, deletion or substitution of at least one base pair. The methods of the present invention offer distinct advantages over other methods of altering the genetic makeup of an organism, in that only the individually targeted bases are altered. No additional foreign DNA sequences are added to the

genetic complement of the organism. Such agents may, for example, be used to develop plants or animals with improved traits by rationally changing the sequence of selected genes in cultured cells. Modified cells are then cloned into whole plants or animals having the altered gene. See, e.g., U.S. Patent 6,046,380 and U.S. Patent 5,905,185 incorporated hererin by reference. Such plants or animals produced using the compositions of the invention lack additional undesirable selectable markers or other foreign DNA sequences. Targeted base pair substitution or frameshift mutations introduced by an oligonucleotide in the presence of a cell-free extract also provides a way to modify the sequence of extrachromosomal elements, including, for example, plasmids, cosmids and artificial chromosomes. The oligonucleotides of the invention also simplify the production of transgenic animals having particular modified or inactivated genes. Altered animal or plant model systems such as those produced using the methods and oligonucleotides of the invention are invaluable in determining the function of a gene and in evaluating drugs. The oligonucleotides and methods of the present invention may also be used for gene therapy to correct mutations causative of human diseases.

The purified oligonucleotide compositions may be formulated in accordance with routine procedures as a pharmaceutical composition adapted for bathing cells in culture, for microinjection into cells in culture, and for intravenous administration to human beings or animals. Typically, compositions for cellular administration or for intravenous administration into animals, including humans, are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anaesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients will be supplied either separately or mixed together in unit dosage form, for example, as a dry, lyophilized powder or water-free concentrate. The composition may be stored in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent in activity units. Where the composition is administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade "water for injection" or saline. Where the composition is to be administered by injection, an ampule of sterile water for injection or saline may be provided so that the ingredients may be mixed prior to administration.

Pharmaceutical compositions of this invention comprise the compounds of the present invention and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable ingredient, excipient, carrier, adjuvant or vehicle.

The oligonucleotides of the invention are preferably administered to the subject in the form of an injectable composition. The composition is preferably administered parenterally, meaning intravenously, intraarterially, intrathecally, interstitially or intracavitarilly. Pharmaceutical compositions of

this invention can be administered to mammals including humans in a manner similar to other diagnostic or therapeutic agents. The dosage to be administered, and the mode of administration will depend on a variety of factors including age, weight, sex, condition of the subject and genetic factors, and will ultimately be decided by medical personnel subsequent to experimental determinations of varying dosage as described herein. In general, dosage required for correction and therapeutic efficacy will range from about 0.001 to 50,000 $\mu\text{g/kg}$, preferably between 1 to 250 $\mu\text{g/kg}$ of host cell or body mass, and most preferably at a concentration of between 30 and 60 micromolar.

For cell administration, direct injection into the nucleus, biolistic bombardment, electroporation, liposome transfer and calcium phosphate precipitation may be used. In yeast, lithium acetate or spheroplast transformation may also be used. In a preferred method, the administration is performed with a liposomal transfer compound, e.g., DOTAP (Boehringer-Mannheim) or an equivalent such as lipofectin. The amount of the oligonucleotide used is about 500 nanograms in 3 micrograms of DOTAP per 100,000 cells. For electroporation, between 20 and 2000 nanograms of oligonucleotide per million cells to be electroporated is an appropriate range of dosages which can be increased to improve efficiency of genetic alteration upon review of the appropriate sequence according to the methods described herein.

Another aspect of the invention is a kit comprising at least one oligonucleotide of the invention. The kit may comprise an addition reagent or article of manufacture. The additional reagent or article of manufacture may comprise a cell extract, a cell, or a plasmid, such as one of those disclosed in the Figures herein, for use in an assay of the invention.

Brief Description Of The Drawings

Figure 1. *Flow diagram for the generation of modified single-stranded oligonucleotides.*

The upper strands of chimeric oligonucleotides I and II are separated into pathways resulting in the generation of single-stranded oligonucleotides that contain (A) 2'-O-methyl RNA nucleotides or (B) phosphorothioate linkages. Fold changes in repair activity for correction of kan^s in the HUH7 cell-free extract are presented in parenthesis. HUH7 cells are described in Nakabayashi et al., Cancer Research 42: 3858-3863 (1982). Each single-stranded oligonucleotide is 25 bases in length and contains a G residue mismatched to the complementary sequence of the kan^s gene. The numbers 3, 6, 8, 10, 12 and 12.5 respectively indicate how many phosphorothioate linkages (S) or 2'-O-methyl RNA nucleotides (R) are at each end of the molecule. Hence oligo 12S/25G contains an all phosphorothioate backbone, displayed as a dotted line. Smooth lines indicate DNA residues, wavy lines indicate 2'-O-methyl RNA

residues and the carat indicates the mismatched base site (G). Figure 1(C) provides a schematic plasmid indicating the sequence of the kan chimeric double-stranded hairpin oligonucleotide (left) and the sequence the tet chimeric double-stranded hairpin oligonucleotide used in other experiments. Figure 1(D) provides a flow chart of a kan experiment in which a chimeric double-stranded hairpin oligonucleotide is used.

Figure 2. *Genetic readout system for correction of a point mutation in plasmid pK^sm4021.*

A mutant kanamycin gene harbored in plasmid pK^sm4021 is the target for correction by oligonucleotides. The mutant G is converted to a C by the action of the oligo. Corrected plasmids confer resistance to kanamycin in *E.coli* (DH10B) after electroporation leading to the genetic readout and colony counts.

Figure 3: *Target plasmid and sequence correction of a frameshift mutation by chimeric and single-stranded oligonucleotides.* (A) Plasmid pT^sΔ208 contains a single base deletion mutation at position 208 rendering it unable to confer tet resistance. The target sequence presented below indicates the insertion of a T directed by the oligonucleotides to re-establish the resistant phenotype. (B) DNA sequence confirming base insertion directed by Tet 3S/25G; the yellow highlight indicates the position of frameshift repair.

Figure 4. *DNA sequences of representative kan^r colonies.* Confirmation of sequence alteration directed by the indicated molecule is presented along with a table outlining codon distribution. Note that 10S/25G and 12S/25G elicit both mixed and unfaithful gene repair. The number of clones sequenced is listed in parentheses next to the designation for the single-stranded oligonucleotide. A plus (+) symbol indicates the codon identified while a figure after the (+) symbol indicates the number of colonies with a particular sequence. TAC/TAG indicates a mixed peak. Representative DNA sequences are presented below the table with yellow highlighting altered residues.

Figure 5. *Gene correction in HeLa cells.* Representative oligonucleotides of the invention are co-transfected with the pCMVneo(+)FIAsH plasmid (shown in Figure 9) into HeLa cells. Ligand is diffused into cells after co-transfection of plasmid and oligonucleotides. Green fluorescence indicates gene correction of the mutation in the antibiotic resistance gene. Correction of the mutation results in the expression of a fusion protein that carries a marker ligand binding site and when the fusion protein binds the ligand, a green fluorescence is emitted. The ligand is produced by Aurora Biosciences and can readily diffuse into cells enabling a measurement of corrected protein function; the protein must bind the ligand directly to induce fluorescence. Hence cells bearing the corrected plasmid gene appear green while "uncorrected" cells remain colorless.

Figure 6. *Z-series imaging of corrected cells*. Serial cross-sections of the HeLa cell represented in Figure 5 are produced by Zeiss 510 LSM confocal microscope revealing that the fusion protein is contained within the cell.

Figure 7. *Hygromycin-eGFP target plasmids*. (A) Plasmid pAURHYG(ins)GFP contains a single base insertion mutation between nucleotides 136 and 137, at codon 46, of the Hygromycin B coding sequence (cgs) which is transcribed from the constitutive ADH1 promoter. The target sequence presented below indicates the deletion of an A and the substitution of a C for a T directed by the oligonucleotides to re-establish the resistant phenotype. (B) Plasmid pAURHYG(rep)GFP contains a base substitution mutation introducing a G at nucleotide 137, at codon 46, of the Hygromycin B coding sequence (cgs). The target sequence presented below the diagram indicates the amino acid conservative replacement of G with C, restoring gene function.

Figure 8. *Oligonucleotides for correction of hygromycin resistance gene*. The sequence of the oligonucleotides used in experiments to assay correction of a hygromycin resistance gene are shown. DNA residues are shown in capital letters, RNA residues are shown in lowercase and nucleotides with a phosphorothioate backbone are capitalized and underlined.

Figure 9. *pAURNeo(-)FIAsH plasmid*. This figure describes the plasmid structure, target sequence, oligonucleotides, and the basis for detection of the gene alteration event by fluorescence.

Figure 10. *pYESHyg(x)eGFP plasmid*. This plasmid is a construct similar to the pAURHyg(x)eGFP construct shown in Figure 7, except the promoter is the inducible GAL1 promoter. This promoter is inducible with galactose, leaky in the presence of raffinose, and repressed in the presence of dextrose.

The following examples are provided by way of illustration only, and are not intended to limit the scope of the invention disclosed herein.

EXAMPLE 1

Assay Method For Base Alteration And Preferred Oligonucleotide Selection

In this example, single-stranded and double-hairpin oligonucleotides with chimeric backbones (see Figure 1 for structures (A and B) and sequences (C and D) of assay oligonucleotides) are used to correct a point mutation in the kanamycin gene of pK^sm4021 (Figure 2) or the tetracycline gene of pT^sΔ208 (Figure 3). All kan oligonucleotides share the same 25 base sequence surrounding the target base identified for change, just as all tet oligonucleotides do. The sequence is given in Figures 1C and Figure 1D. Each plasmid contains a functional ampicillin gene. Kanamycin gene function is restored

when a G at position 4021 is converted to a C (via a substitution mutation); tetracycline gene function is restored when a deletion at position 208 is replaced by a C (via frameshift mutation). A separate plasmid, pAURNeo(-)FIAsH (Figure 9), bearing the kan^s gene is used in the cell culture experiments. This plasmid was constructed by inserting a synthetic expression cassette containing a neomycin phosphotransferase (kanamycin resistance) gene and an extended reading frame that encodes a receptor for the FIAsH ligand into the pAUR123 shuttle vector (Panvera Corp., Madison, WI). The resulting construct replicates in *S. cerevisiae* at low copy number, confers resistance to aureobasidinA and constitutively expresses either the Neo+/FIAsH fusion product (after alteration) or the truncated Neo-/FIAsH product (before alteration) from the ADH1 promoter. By extending the reading frame of this gene to code for a unique peptide sequence capable of binding a small ligand to form a fluorescent complex, restoration of expression by correction of the stop codon can be detected in real time using confocal microscopy. Additional constructs can be made to test additional gene alteration events.

We also construct three mammalian expression vectors, pHyg(rep)eGFP, pHyg(Δ)eGFP, pHyg(ins)eGFP, that contain a substitution mutation at nucleotide 137 of the hygromycin-B coding sequence. (rep) indicates a T137→G replacement, (Δ) represents a deletion of the G137 and (ins) represents an A insertion between nucleotides 136 and 137. All point mutations create a nonsense termination codon at residue 46. We use pHygEGFP plasmid (Invitrogen, CA) DNA as a template to introduce the mutations into the hygromycin-eGFP fusion gene by a two step site-directed mutagenesis PCR protocol. First, we generate overlapping 5' and a 3' amplicons surrounding the mutation site by PCR for each of the point mutation sites. A 215 bp 5' amplicon for the (rep), (Δ) or (ins) was generated by polymerization from oligonucleotide primer HygEGFPf (5'-AATACGACTCACTATAGG-3') to primer Hygrepr (5'-GACCTATCCACGCCCTCC-3'), Hyg Δ r (5'-GACTATCCACGCCCTCC-3'), or Hyginsr (5'-GACATTATCCACGCCCTCC-3'), respectively. We generate a 300bp 3' amplicon for the (rep), (Δ) or (ins) by polymerization from oligonucleotide primers Hygrepf (5'-CTGGGATAGGTCCTGCGG-3'), Hyg Δ f (5'-CGTGGATAGTCCTGCGG-3'), Hyginsf (5'-CGTGGATAATGTCCTGCGG-3'), respectively to primer HygEGFPf (5'-AAATCACGCCATGTAGTG-3'). We mix 20 ng of each of the resultant 5' and 3' overlapping amplicon mutation sets and use the mixture as a template to amplify a 523 bp fragment of the Hygromycin gene spanning the KpnI and RsrII restriction endonuclease sites. We use the Expand PCR system (Roche) to generate all amplicons with 25 cycles of denaturing at 94°C for 10 seconds, annealing at 55°C for 20 seconds and elongation at 68°C for 1 minute. We digest 10 μ g of vector pHygEGFP and 5 μ g of the resulting fragments for each mutation with KpnI and RsrII (NEB) and gel purify the fragment for enzymatic ligation. We ligate each mutated insert into pHygEGFP vector at 3:1 molar ration using T4

DNA ligase (Roche). We screen clones by restriction digest, confirm the mutation by Sanger dideoxy chain termination sequencing and purify the plasmid using a Qiagen maxiprep kit.

Oligonucleotide synthesis and cells. Chimeric oligonucleotides and single-stranded oligonucleotides (including those with the indicated modifications) are synthesized using available phosphoramidites on controlled pore glass supports. After deprotection and detachment from the solid support, each oligonucleotide is gel-purified using, for example, procedures such as those described in Gamper *et al.*, *Biochem.* 39, 5808-5816 (2000) and the concentrations determined spectrophotometrically (33 or 40 µg/ml per A₂₆₀ unit of single-stranded or hairpin oligomer). HUH7 cells are grown in DMEM, 10% FBS, 2mM glutamine, 0.5% pen/strep. The *E.coli* strain, DH10B, is obtained from Life Technologies (Gaithersburg, MD); DH10B cells contain a mutation in the RECA gene (*recA*).

Cell-free extracts. We prepare cell-free extracts from HUH7 cells or other mammalian cells, as follows. We employ this protocol with essentially any mammalian cell including, for example, H1299 cells (human epithelial carcinoma, non-small cell lung cancer), C1271 (immortal murine mammary epithelial cells), MEF (mouse embryonic fibroblasts), HEC-1-A (human uterine carcinoma), HCT15 (human colon cancer), HCT116 (human colon carcinoma), LoVo (human colon adenocarcinoma), and HeLa (human cervical carcinoma). We harvest approximately 2x10⁸ cells. We then wash the cells immediately in cold hypotonic buffer (20 mM HEPES, pH7.5; 5 mM KCl; 1.5 mM MgCl₂; 1 mM DTT) with 250 mM sucrose. We then resuspend the cells in cold hypotonic buffer without sucrose and after 15 minutes we lyse the cells with 25 strokes of a Dounce homogenizer using a tight fitting pestle. We incubate the lysed cells for 60 minutes on ice and centrifuge the sample for 15 minutes at 12000xg. The cytoplasmic fraction is enriched with nuclear proteins due to the extended co-incubation of the fractions following cell breakage. We then immediately aliquote and freeze the supernatant at -80°C. We determine the protein concentration in the extract by the Bradford assay.

We also perform these experiments with cell-free extracts obtained from fungal cells, including, for example, *S. cerevisiae* (yeast), *Ustilago maydis*, and *Candida albicans*. For example, we grow yeast cells into log phase in 2L YPD medium for 3 days at 30°C. We then centrifuge the cultures at 5000xg, resuspend the pellets in a 10% sucrose, 50 mM Tris, 1mM EDTA lysis solution and freeze them on dry ice. After thawing, we add KCl, spermidine and lyticase to final concentrations of 0.25 mM, 5 mM and 0.1 mg/ml, respectively. We incubate the suspension on ice for 60 minutes, add PMSF and Triton X100 to final concentrations of 0.1 mM and 0.1% and continue to incubate on ice for 20 minutes. We centrifuge the lysate at 3000xg for 10 minutes to remove larger debris. We then remove the supernatant and clarify it by centrifuging at 30000xg for 15 minutes. We then add glycerol to the clarified extract to a

concentration of 10% (v/v) and freeze aliquots at -80°C. We determine the protein concentration of the extract by the Bradford assay.

Reaction mixtures of 50 µl are used, consisting of 10-30 µg protein of cell-free extract, which can be optionally substituted with purified proteins or enriched fractions, about 1.5 µg chimeric double-hairpin oligonucleotide or 0.55 µg single-stranded molecule (3S/25G or 6S/25G, see Figure 1), and 1 µg of plasmid DNA (see Figures 2 and 3) in a reaction buffer of 20 mM Tris, pH 7.4, 15 mM MgCl₂, 0.4 mM DTT, and 1.0 mM ATP. Reactions are initiated with extract and incubated at 30°C for 45 min. The reaction is stopped by placing the tubes on ice and then immediately deproteinized by two phenol/chloroform (1:1) extractions. Samples are then ethanol precipitated. The nucleic acid is pelleted at 15,000 r.p.m. at 4°C for 30 min., is washed with 70% ethanol, resuspended in 50 µl H₂O, and is stored at -20°C. 5 µl of plasmid from the resuspension (~100 ng) was transfected in 20 µl of DH10B cells by electroporation (400 V, 300 µF, 4 kΩ) in a Cell-Porator apparatus (Life Technologies). After electroporation, cells are transferred to a 14 ml Falcon snap-cap tube with 2 ml SOC and shaken at 37°C for 1 h. Enhancement of final kan colony counts is achieved by then adding 3 ml SOC with 10 µg/ml kanamycin and the cell suspension is shaken for a further 2 h at 37°C. Cells are then spun down at 3750 x g and the pellet is resuspended in 500 µl SOC. 200 µl is added undiluted to each of two kanamycin (50 µg/ml) agar plates and 200 µl of a 10⁵ dilution is added to an ampicillin (100 µg/ml) plate. After overnight 37°C incubation, bacterial colonies are counted using an Accucount 1000 (Biologics). Gene conversion effectiveness is measured as the ratio of the average of the kan colonies on both plates per amp colonies multiplied by 10⁻⁵ to correct for the amp dilution.

The following procedure can also be used. 5 µl of resuspended reaction mixtures (total volume 50 µl) are used to transform 20 µl aliquots of electro-competent ΔH10B bacteria using a Cell-Porator apparatus (Life Technologies). The mixtures are allowed to recover in 1 ml SOC at 37°C for 1 hour at which time 50 µg/ml kanamycin or 12 µg/ml tetracycline is added for an additional 3 hours. Prior to plating, the bacteria are pelleted and resuspended in 200 µl of SOC. 100 µl aliquots are plated onto kan or tet agar plates and 100 µl of a 10⁻⁴ dilution of the cultures are concurrently plated on agar plates containing 100 µg/ml of ampicillin. Plating is performed in triplicate using sterile Pyrex beads. Colony counts are determined by an Accu-count 1000 plate reader (Biologics). Each plate contains 200-500 ampicillin resistant colonies or 0-500 tetracycline or kanamycin resistant colonies. Resistant colonies are selected for plasmid extraction and DNA sequencing using an ABI Prism kit on an ABI 310 capillary sequencer (PE Biosystems).

Chimeric single-stranded oligonucleotides. In Figure 1 the upper strands of chimeric oligonucleotides I and II are separated into pathways resulting in the generation of single-stranded oligonucleotides that contain (Figure 1A) 2'-O-methyl RNA nucleotides or (Figure 1B) phosphorothioate linkages. Fold changes in repair activity for correction of kan^s in the HUH7 cell-free extract are presented in parenthesis. Each single-stranded oligonucleotide is 25 bases in length and contains a G residue mismatched to the complementary sequence of the kan^s gene.

Molecules bearing 3, 6, 8, 10 and 12 phosphorothioate linkages in the terminal regions at each end of a backbone with a total of 24 linkages (25 bases) are tested in the kan^s system. Alternatively, molecules bearing 2, 4, 5, 7, 9 and 11 in the terminal regions at each end are tested. The results of one such experiment, presented in Table 1 and Figure 1B, illustrate an enhancement of correction activity directed by some of these modified structures. In this illustrative example, the most efficient molecules contained 3 or 6 phosphorothioate linkages at each end of the 25-mer; the activities are approximately equal (molecules IX and X with results of 3.09 and 3.7 respectively). A reduction in alteration activity may be observed as the number of modified linkages in the molecule is further increased. Interestingly, a single-strand molecule containing 24 phosphorothioate linkages is minimally active suggesting that this backbone modification when used throughout the molecule supports only a low level of targeted gene repair or alteration. Such a non-altering, completely modified molecule can provide a baseline control for determining efficiency of correction for a specific oligonucleotide molecule of known sequence in defining the optimum oligonucleotide for a particular alteration event.

The efficiency of gene repair directed by phosphorothioate-modified, single-stranded molecules, in a length dependent fashion, led us to examine the length of the RNA modification used in the original chimera as it relates to correction. Construct III represents the "RNA-containing" strand of chimera I and, as shown in Table 1 and Figure 2A, it promotes inefficient gene repair. But, as shown in the same figure, reducing the RNA residues on each end from 10 to 3 increases the frequency of repair. At equal levels of modification, however, 25-mers with 2'-O-methyl ribonucleotides were less effective gene repair agents than the same oligomers with phosphorothioate linkages. These results reinforce the fact that an RNA containing oligonucleotide is not as effective in promoting gene repair or alteration as a modified DNA oligonucleotide.

Repair of the kanamycin mutation requires a G→C exchange. To confirm that the specific desired correction alteration was obtained, colonies selected at random from multiple experiments are processed and the isolated plasmid DNA is sequenced. As seen in Figure 4, colonies generated through the action of the single-stranded molecules 3S/25G (IX), 6S/25G (X) and 8S/25G (XI) respectively

contained plasmid molecules harboring the targeted base correction. While a few colonies appeared on plates derived from reaction mixtures containing 25-mers with 10 or 12 thioate linkages on both ends, the sequences of the plasmid molecules from these colonies contain nonspecific base changes. In these illustrative examples, the second base of the codon is changed (see Figure 3). These results show that modified single-strands can direct gene repair, but that efficiency and specificity are reduced when the 25-mers contain 10 or more phosphorothioate linkages at each end.

In Figure 1, the numbers 3, 6, 8, 10, 12 and 12.5 respectively indicate how many phosphorothioate linkages (S) or 2'-O-methyl RNA nucleotides (R) are at each end of the exemplified molecule although other molecules with 2, 4, 5, 7, 9 and 11 modifications at each end can also be tested. Hence oligo 12S/25G represents a 25-mer oligonucleotide which contains 12 phosphorothioate linkages on each side of the central G target mismatch base producing a fully phosphorothioate linked backbone, displayed as a dotted line. The dots are merely representative of a linkage in the figure and do not depict the actual number of linkages of the oligonucleotide. Smooth lines indicate DNA residues, wavy lines indicate 2'-O-methyl RNA residues and the carat indicates the mismatched base site (G).

Correction of a mutant kanamycin gene in cultured mammalian cells. The experiments are performed using different mammalian cells, including, for example, 293 cells (transformed human primary kidney cells), HeLa cells (human cervical carcinoma), and H1299 (human epithelial carcinoma, non-small cell lung cancer). HeLa cells are grown at 37°C and 5% CO₂ in a humidified incubator to a density of 2 x 10⁵ cells/ml in an 8 chamber slide (Lab-Tek). After replacing the regular DMEM with Optimem, the cells are co-transfected with 10 µg of plasmid pAURNeo(-)FIAsH and 5 µg of modified single-stranded oligonucleotide (3S/25G) that is previously complexed with 10 µg lipofectamine, according to the manufacturer's directions (Life Technologies). The cells are treated with the liposome-DNA-oligo mix for 6 hrs at 37°C. Treated cells are washed with PBS and fresh DMEM is added. After a 16-18 hr recovery period, the culture is assayed for gene repair. The same oligonucleotide used in the cell-free extract experiments is used to target transfected plasmid bearing the kan^s gene. Correction of the point mutation in this gene eliminates a stop codon and restores full expression. This expression can be detected by adding a small non-fluorescent ligand that bound to a C-C-R-E-C-C sequence in the genetically modified carboxy terminus of the kan protein, to produce a highly fluorescent complex (FIAsH system, Aurora Biosciences Corporation). Following a 60 min incubation at room temperature with the ligand (FIAsH-EDT2), cells expressing full length kan product acquire an intense green fluorescence detectable by fluorescence microscopy using a fluorescein filter set. Similar experiments are performed using the HygeGFP target as described in Example 2 with a variety of mammalian cells, including, for

example, COS-1 and COS-7 cells (African green monkey), and CHO-K1 cells (Chinese hamster ovary). The experiments are also performed with PG12 cells (rat pheochromocytoma) and ES cells (human embryonic stem cells).

Summary of experimental results. Tables 1, 2 and 3 respectively provide data on the efficiency of gene repair directed by single-stranded oligonucleotides. Table 1 presents data using a cell-free extract from human liver cells (HUH7) to catalyze repair of the point mutation in plasmid pkan^sm4021 (see Figure 1). Table 2 illustrates that the oligomers are not dependent on MSH2 or MSH3 for optimal gene repair activity. Table 3 illustrates data from the repair of a frameshift mutation (Figure 3) in the tet gene contained in plasmid pTetΔ208. Table 4 illustrates data from repair of the pkan^sm4021 point mutation catalyzed by plant cell extracts prepared from canola and musa (banana). Colony numbers are presented as kan^r or tet^r and fold increases (single strand versus double hairpin) are presented for kan^r in Table 1.

Figure 5A is a confocal picture of HeLa cells expressing the corrected fusion protein from an episomal target. Gene repair is accomplished by the action of a modified single-stranded oligonucleotide containing 3 phosphorothioate linkages at each end (3S/25G). Figure 5B represents a "Z-series" of HeLa cells bearing the corrected fusion gene. This series sections the cells from bottom to top and illustrates that the fluorescent signal is "inside the cells".

Results. In summary, we have designed a novel class of single-stranded oligonucleotides with backbone modifications at the termini and demonstrate gene repair/conversion activity in mammalian and plant cell-free extracts. We confirm that the all DNA strand of the RNA-DNA double-stranded double hairpin chimera is the active component in the process of gene repair. In some cases, the relative frequency of repair by the novel oligonucleotides of the invention is elevated approximately 3-4-fold when compared to frequencies directed by chimeric RNA-DNA double hairpin oligonucleotides.

This strategy centers around the use of extracts from various sources to correct a mutation in a plasmid using a modified single-stranded or a chimeric RNA-DNA double hairpin oligonucleotide. A mutation is placed inside the coding region of a gene conferring antibiotic resistance in bacteria, here kanamycin or tetracycline. The appearance of resistance is measured by genetic readout in *E.coli* grown in the presence of the specified antibiotic. The importance of this system is that both phenotypic alteration and genetic inheritance can be measured. Plasmid pK^sm4021 contains a mutation (T→G) at residue 4021 rendering it unable to confer antibiotic resistance in *E.coli*. This point mutation is targeted for repair by oligonucleotides designed to restore kanamycin resistance. To avoid concerns of

plasmid contamination skewing the colony counts, the directed correction is from G→C rather than G→T (wild-type). After isolation, the plasmid is electroporated into the DH10B strain of *E.coli*, which contains inactive RecA protein. The number of kanamycin colonies is counted and normalized by ascertaining the number of ampicillin colonies, a process that controls for the influence of electroporation. The number of colonies generated from three to five independent reactions was averaged and is presented for each experiment. A fold increase number is recorded to aid in comparison.

The original RNA-DNA double hairpin chimera design, e.g., as disclosed in U.S. Patent 5,565,350, consists of two hybridized regions of a single-stranded oligonucleotide folded into a double hairpin configuration. The double-stranded targeting region is made up of a 5 base pair DNA/DNA segment bracketed by 10 base pair RNA/DNA segments. The central base pair is mismatched to the corresponding base pair in the target gene. When a molecule of this design is used to correct the *kan^s* mutation, gene repair is observed (I in Figure 1A). Chimera II (Figure 1B) differs partly from chimera I in that only the DNA strand of the double hairpin is mismatched to the target sequence. When this chimera was used to correct the *kan^s* mutation, it was twice as active. In the same study, repair function could be further increased by making the targeting region of the chimera a continuous RNA/DNA hybrid.

Frame shift mutations are repaired. By using plasmid pT^sΔ208, described in Figure 1(C) and Figure 3, the capacity of the modified single-stranded molecules that showed activity in correcting a point mutation, can be tested for repair of a frameshift. To determine efficiency of correction of the mutation, a chimeric oligonucleotide (Tet I), which is designed to insert a T residue at position 208, is used. A modified single-stranded oligonucleotide (Tet IX) directs the insertion of a T residue at this same site. Figure 3 illustrates the plasmid and target bases designated for change in the experiments. When all reaction components are present (extract, plasmid, oligomer), tetracycline resistant colonies appear. The colony count increases with the amount of oligonucleotide used up to a point beyond which the count falls off (Table 3). No colonies above background are observed in the absence of either extract or oligonucleotide, nor when a modified single-stranded molecule bearing perfect complementarity is used. Figure 3 represents the sequence surrounding the target site and shows that a T residue is inserted at the correct site. We have isolated plasmids from fifteen colonies obtained in three independent experiments and each analyzed sequence revealed the same precise nucleotide insertion. These data suggest that the single-stranded molecules used initially for point mutation correction can also repair nucleotide deletions.

Comparison of phosphorothioate oligonucleotides to 2'-O-methyl substituted oligonucleotides. From a comparison of molecules VII and XI, it is apparent that gene repair is more

subject to inhibition by RNA residues than by phosphorothioate linkages. Thus, even though both of these oligonucleotides contain an equal number of modifications to impart nuclease resistance, XI (with 16 phosphorothioate linkages) has good gene repair activity while VII (with 16 2'-O-methyl RNA residues) is inactive. Hence, the original chimeric double hairpin oligonucleotide enabled correction directed, in large part, by the strand containing a large region of contiguous DNA residues.

Oligonucleotides can target multiple nucleotide alterations within the same template. The ability of individual single-stranded oligonucleotides to correct multiple mutations in a single target template is tested using the plasmid pK^sm4021 and the following single-stranded oligonucleotides modified with 3 phosphorothioate linkages at each end (indicated as underlined nucleotides): Oligo1 is a 25-mer with the sequence TTCGATAAGCCTATGCTGACCCGTG corrects the original mutation present in the kanamycin resistance gene of pK^sm4021 as well as directing another alteration 2 basepairs away in the target sequence (both indicated in boldface); Oligo2 is a 70-mer with the 5'-end sequence TTCGGCTACGACTGGGCACAACAGACAATTGGC with the remaining nucleotides being completely complementary to the kanamycin resistance gene and also ending in 3 phosphorothioate linkages at the 3' end. Oligo2 directs correction of the mutation in pK^sm4021 as well as directing another alteration 21 basepairs away in the target sequence (both indicated in boldface).

We also use additional oligonucleotides to assay the ability of individual oligonucleotides to correct multiple mutations in the pK^sM4021 plasmid. These include, for example, a second 25-mer that alters two nucleotides that are three nucleotides apart with the sequence 5'-TTGTGCCCAGTCGTAICCGAATAGC-3'; a 70-mer that alters two nucleotides that are 21 nucleotides apart with the sequence 5'-CATCAGAGCAGCCAATTGTCTGTTGTGCCCAGTCGTAGCCGAA TAGCCTCTCCACCCAAGCGGCCGGAGA-3'; and another 70-mer that alters two nucleotides that are 21 nucleotides apart with the sequence 5'-GCTGACAGCCGGAACACGGCGGCATCAGAGCAGCCAATTGTCTGTTGTGCCCAGTCGTAGCCGAAT AGCCT-3'. The nucleotides in the oligonucleotides that direct alteration of the target sequence are underlined and in boldface. These oligonucleotides are modified in the same way as the other oligonucleotides of the invention.

We assay correction of the original mutation in pK^sm4021 by monitoring kanamycin resistance (the second alterations which are directed by Oligo2 and Oligo3 are silent with respect to the kanamycin resistance phenotype). In addition, in experiments with Oligo2, we also monitor cleavage of the resulting plasmids using the restriction enzyme Tsp509I which cuts at a specific site present only when the second alteration has occurred (at ATT in Oligo2). We then sequence these clones to

determine whether the additional, silent alteration has also been introduced. The results of an analysis are presented below:

	Oligo1 (25-mer)	Oligo2 (70-mer)
Clones with both sites changed	9	7
Clones with a single site changed	0	2
Clones that were not changed	4	1

Nuclease sensitivity of unmodified DNA oligonucleotide. Electrophoretic analysis of nucleic acid recovered from the cell-free extract reactions conducted here confirm that the unmodified single-stranded 25-mer did not survive incubation whereas greater than 90% of the terminally modified oligos did survive (as judged by photo-image analyses of agarose gels).

Plant extracts direct repair. The modified single-stranded constructs can be tested in plant cell extracts. We have observed gene alteration using extracts from multiple plant sources, including, for example, Arabidopsis, tobacco, banana, maize, soybean, canola, wheat, spinach as well as spinach chloroplast extract. We prepare the extracts by grinding plant tissue or cultured cells under liquid nitrogen with a mortar and pestle. We extract 3 ml of the ground plant tissue with 1.5 ml of extraction buffer (20 mM HEPES, pH7.5; 5 mM KCl; 1.5 mM MgCl₂; 10 mM DTT; 10% [v/v] glycerol; and 1 % [w/v] PVP). We then homogenize the samples with 15 strokes of a Dounce homogenizer. Following homogenization, we incubate the samples on ice for 1 hour and centrifuge at 3000xg for 5 minutes to remove plant cell debris. We then determine the protein concentration in the supernatants (extracts) by Bradford assay. We dispense 100 µg (protein) aliquots of the extracts which we freeze in a dry ice-ethanol bath and store at -80°C.

We describe experiments using two sources here: a dicot (canola) and a monocot (banana, *Musa acuminata* cv. Rasthali). Each vector directs gene repair of the kanamycin mutation (Table 4); however, the level of correction is elevated 2-3 fold relative to the frequency observed with the chimeric oligonucleotide. These results are similar to those observed in the mammalian system wherein a significant improvement in gene repair occurred when modified single-stranded molecules were used.

Tables are attached hereto.

Table I

Gene repair activity is directed by single-stranded oligonucleotides.

Oligonucleotide	Plasmid	Extract (ug)	kan ^r colonies	Fold increase
I	pK ^s m4021	10	300	
I		20	418	1.0x
II		10	537	
II		20	748	1.78x
III		10	3	
III		20	5	0.01x
IV		10	112	
IV		20	96	0.22x
V		10	217	
V		20	342	0.81x
VI		10	6	
VI		20	39	0.093x
VII		10	0	
VII		20	0	0x
VIII		10	3	
VIII		20	5	0.01x
IX		10	936	
IX		20	1295	3.09x
X		10	1140	
X		20	1588	3.7x
XI		10	480	
XI		20	681	1.6x
XII		10	18	
XII		20	25	0.059x
XIII		10	0	
XIII		20	4	0.009x
-		20	0	
I		-	0	

Plasmid pK^sm4021 (1μg), the indicated oligonucleotide (1.5 μg chimeric oligonucleotide or 0.55 μg single-stranded oligonucleotide; molar ratio of oligo to plasmid of 360 to 1) and either 10 or 20 μg of HUH7 cell-free extract were incubated 45 min at 37°C. Isolated plasmid DNA was electroporated into *E. coli* (strain DH10B) and the number of kan^r colonies counted. The data represent the number of kanamycin resistant colonies per 10⁶ ampicillin resistant colonies generated from the same reaction and is the average of three

experiments (standard deviation usually less than +/- 15%). Fold increase is defined relative to 418 kan^r colonies (second reaction) and in all reactions was calculated using the 20µg sample.

Table II

Modified single-stranded oligomers are not dependent on MSH2 or MSH3 for optimal gene repair activity.

A. Oligonucleotide	Plasmid	Extract	kan ^r colonies
IX (3S/25G)	↓	HUH7	637
X (6S/25G)		HUH7	836
IX		MEF2 ^{-/-}	781
X		MEF2 ^{-/-}	676
IX		MEF3 ^{-/-}	582
X		MEF3 ^{-/-}	530
IX		MEF ^{+/+}	332
X		MEF ^{+/+}	497
-		MEF2 ^{-/-}	10
-		MEF3 ^{-/-}	5
-		MEF ^{+/+}	14

Chimeric oligonucleotide (1.5 µg) or modified single-stranded oligonucleotide (0.55 µg) was incubated with 1 µg of plasmid pK^sm4021 and 20 µg of the indicated extracts. MEF represents mouse embryonic fibroblasts with either MSH2 (2^{-/-}) or MSH3 (3^{-/-}) deleted. MEF^{+/+} indicates wild-type mouse embryonic fibroblasts. The other reaction components were then added and processed through the bacterial readout system. The data represent the number of kanamycin resistant colonies per 10⁶ ampicillin resistant colonies.

Table III

Frameshift mutation repair is directed by single-stranded oligonucleotides

Oligonucleotide	Plasmid	Extract	tet ^r colonies
Tet IX (3S/25A; 0.5 µg)	pT ^s Δ208 (1 µg)	-	0
-	↓	20µg	0
Tet IX (0.5 µg)		↓	48
Tet IX (1.5 µg)			130
Tet IX (2.0 µg)			68
Tet I (chimera; 1.5 µg)		↓	48

Each reaction mixture contained the indicated amounts of plasmid and oligonucleotide.

The extract used for these experiments came from HUH7 cells. The data represent the number of tetracycline resistant colonies per 10⁶ ampicillin resistant colonies generated from the same reaction and is the average of 3 independent experiments. Tet I is a chimeric oligonucleotide and Tet IX is a modified single-stranded oligonucleotide that are designed to insert a T residue at position 208 of pT^sΔ208. These oligonucleotides are equivalent to structures I and IX in Figure 2.

Table IV

Plant cell-free extracts support gene repair by single-stranded oligonucleotides

Oligonucleotide	Plasmid	Extract	kan ^r colonies
II (chimera)	pK ^S m4021	30µg Canola	337
IX (3S/25G)	↓	Canola	763
X (6S/25G)		Canola	882
II		<i>Musa</i>	203
IX		<i>Musa</i>	343
X		<i>Musa</i>	746
-		Canola	0
-		<i>Musa</i>	0
IX		- Canola	0
X		- <i>Musa</i>	0

Canola or *Musa* cell-free extracts were tested for gene repair activity on the kanamycin-sensitive gene as previously described in (18). Chimeric oligonucleotide II (1.5 µg) and modified single-stranded oligonucleotides IX and X (0.55µg) were used to correct pK^Sm4021. Total number of kan^r colonies are present per 10⁷ ampicillin resistant colonies and represent an average of four independent experiments.

Table V
Gene repair activity in cell-free extracts prepared from yeast (Saccharomyces cerevisiae)

Cell-type	Plasmid	Chimeric Oligo	SS Oligo	kan ^r /amp ^r × 10 ⁶
Wild type	pKan ^r m4021	1μg		0.36
Wild type	↓		1μg	0.81
ΔRAD52		1μg		10.72
ΔRAD52			1μg	17.41
ΔPMS1		1μg		2.02
ΔPMS1			1μg	3.23

In this experiment, the kan^r gene in pKan^r4021 is corrected by either a chimeric double-hairpin oligonucleotide or a single-stranded oligonucleotide containing three thioate linkages at each end (3S/25G).

EXAMPLE 2

Yeast Cell Targeting Assay Method for Base Alteration and Preferred Oligonucleotide Selection

In this example, single-stranded oligonucleotides with modified backbones and double-hairpin oligonucleotides with chimeric, RNA-DNA backbones are used to measure gene repair using two episomal targets with a fusion between a hygromycin resistance gene and eGFP as a target for gene repair. These plasmids are pAURHYG(rep)GFP, which contains a point mutation in the hygromycin resistance gene (Figure 7), pAURHYG(ins)GFP, which contains a single-base insertion in the hygromycin resistance gene (Figure 7) and pAURHYG(Δ)GFP which has a single base deletion. We also use the plasmid containing a wild-type copy of the hygromycin-eGFP fusion gene, designated pAURHYG(wt)GFP, as a control. These plasmids also contain an aureobasidinA resistance gene. In pAURHYG(rep)GFP, hygromycin resistance gene function and green fluorescence from the eGFP protein are restored when a G at position 137, at codon 46 of the hygromycin B coding sequence, is converted to a C thus removing a premature stop codon in the hygromycin resistance gene coding region. In pAURHYG(ins)GFP, hygromycin resistance gene function and green fluorescence from the eGFP protein are restored when an A inserted between nucleotide positions 136 and 137, at codon 46 of the hygromycin B coding sequence, is deleted and a C is substituted for the T at position 137, thus correcting a frameshift mutation and restoring the reading frame of the hygromycin-eGFP fusion gene.

We synthesize the set of three yeast expression constructs pAURHYG(rep)eGFP, pAURHYG(Δ)eGFP, pAURHYG(ins)eGFP, that contain a point mutation at nucleotide 137 of the hygromycin-B coding sequence as follows. (rep) indicates a T137 \rightarrow G replacement, (Δ) represents a deletion of the G137 and (ins) represents an A insertion between nucleotides 136 and 137. We construct this set of plasmids by excising the respective expression cassettes by restriction digest from pHyg(x)EGFP and ligation into pAUR123 (Panvera, CA). We digest 10 μ g pAUR123 vector DNA, as well as, 10 μ g of each pHyg(x)EGFP construct with KpnI and Sall (NEB). We gel purify each of the DNA fragments and prepare them for enzymatic ligation. We ligate each mutated insert into pHygEGFP vector at 3:1 molar ratio using T4 DNA ligase (Roche). We screen clones by restriction digest, confirm by Sanger dideoxy chain termination sequencing and purify using a Qiagen maxiprep kit.

We use this system to assay the ability of five oligonucleotides (shown in Figure 8) to support correction under a variety of conditions. The oligonucleotides which direct correction of the mutation in pAURHYG(rep)GFP can also direct correction of the mutation in pAURHYG(ins)GFP. Three of the four oligonucleotides (HygE3T/25, HygE3T/74 and HygGG/Rev) share the same 25-base sequence surrounding the base targeted for alteration. HygGG/Rev is an RNA-DNA chimeric double hairpin

oligonucleotide of the type described in the prior art. One of these oligonucleotides, HygE3T/74, is a 74-base oligonucleotide with the 25-base sequence centrally positioned. The fourth oligonucleotide, designated HygE3T/74 α , is the reverse complement of HygE3T/74. The fifth oligonucleotide, designated Kan70T, is a non-specific, control oligonucleotide which is not complementary to the target sequence.

5 Alternatively, an oligonucleotide of identical sequence but lacking a mismatch to the target or a completely thioate modified oligonucleotide or a completely 2-O-methylated modified oligonucleotide may be used as a control.

Oligonucleotide synthesis and cells. We synthesized and purified the chimeric, double-hairpin oligonucleotides and single-stranded oligonucleotides (including those with the indicated modifications) as described in Example 1. Plasmids used for assay were maintained stably in yeast (10 *Saccharomyces cerevisiae*) strain LSY678 MAT α at low copy number under aureobasidin selection. Plasmids and oligonucleotides are introduced into yeast cells by electroporation as follows: to prepare electrocompetent yeast cells, we inoculate 10 ml of YPD media from a single colony and grow the cultures overnight with shaking at 300 rpm at 30°C. We then add 30 ml of fresh YPD media to the overnight cultures and continue shaking at 30°C until the OD₆₀₀ was between 0.5 and 1.0 (3-5 hours). We (15 then wash the cells by centrifuging at 4°C at 3000 rpm for 5 minutes and twice resuspending the cells in 25 ml ice-cold distilled water. We then centrifuge at 4°C at 3000 rpm for 5 minutes and resuspend in 1 ml ice-cold 1M sorbitol and then finally centrifuge the cells at 4°C at 5000 rpm for 5 minutes and resuspend the cells in 120 μ l 1M sorbitol. To transform electrocompetent cells with plasmids or oligonucleotides, we (20 mix 40 μ l of cells with 5 μ g of nucleic acid, unless otherwise stated, and incubate on ice for 5 minutes. We then transfer the mixture to a 0.2 cm electroporation cuvette and electroporate with a BIO-RAD Gene Pulser apparatus at 1.5 kV, 25 μ F, 200 Ω for one five-second pulse. We then immediately resuspend the cells in 1 ml YPD supplemented with 1M sorbitol and incubate the cultures at 30°C with shaking at 300 rpm for 6 hours. We then spread 200 μ l of this culture on selective plates containing 300 μ g/ml (25 hygromycin and spread 200 μ l of a 10⁵ dilution of this culture on selective plates containing 500 ng/ml aureobasidinA and/or and incubate at 30°C for 3 days to allow individual yeast colonies to grow. We then count the colonies on the plates and calculate the gene conversion efficiency by determining the number of hygromycin resistance colonies per 10⁵ aureobasidinA resistant colonies.

Frameshift mutations are repaired in yeast cells. We test the ability of the (30 oligonucleotides shown in Figure 8 to correct a frameshift mutation *in vivo* using LSY678 yeast cells containing the plasmid pAURHYG(ins)GFP. These experiments, presented in Table 6, indicate that these oligonucleotides can support gene correction in yeast cells. These data reinforce the results described in

Example 1 indicating that oligonucleotides comprising phosphorothioate linkages facilitate gene correction much more efficiently than control duplex, chimeric RNA-DNA oligonucleotides. This gene correction activity is also specific as transformation of cells with the control oligonucleotide Kan70T produced no hygromycin resistant colonies above background and thus Kan70T did not support gene correction in this system. In addition, we observe that the 74-base oligonucleotide (HygE3T/74) corrects the mutation in pAURHYG(ins)GFP approximately five-fold more efficiently than the 25-base oligonucleotide (HygE3T/25). We also perform control experiments with LSY678 yeast cells containing the plasmid pAURHYG(wt)GFP. With this strain we observed that even without added oligonucleotides, there are too many hygromycin resistant colonies to count.

We also use additional oligonucleotides to assay the ability of individual oligonucleotides to correct multiple mutations in the pAURHYG(x)eGFP plasmid. These include, for example, one that alters two basepairs that are 3 nucleotides apart is a 74-mer with the sequence 5'-CTCGTGCTTTCAGCTTCGATGTAGGAGGGCGTGGG**TAC**CGTCCTGCGGGTAAATAGCTGCGCCGATGTTTCTAC-3'; a 74-mer that alters two basepairs that are 15 nucleotides apart with the sequence 5'-CTCGTGCTTTCAGCTTCGATGTAGGAGGGCGTGGATA**CGT**CCTGCGGGTAAACAGCTGCGCCGATGTTTCTAC-3'; and a 74-mer that alters two basepairs that are 27 nucleotides apart with the sequence 5'-CTCGTGCTTTCAGCTTCGATGTAGGAGGGCGTGGATA**CGT**CCTGCGGGTAAATAGCTGCGCCGAC**G**GTTTCTAC. The nucleotides in these oligonucleotides that direct alteration of the target sequence are underlined and in boldface. These oligonucleotides are modified in the same ways as the other oligonucleotides of the invention.

Oligonucleotides targeting the sense strand direct gene correction more efficiently. We compare the ability of single-stranded oligonucleotides to target each of the two strands of the target sequence of both pAURHYG(ins)GFP and pAURHYG(rep)GFP. These experiments, presented in Tables 7 and 8, indicate that an oligonucleotide, HygE3T/74 α , with sequence complementary to the sense strand (i.e. the strand of the target sequence that is identical to the mRNA) of the target sequence facilitates gene correction approximately ten-fold more efficiently than an oligonucleotide, HygE3T/74, with sequence complementary to the non-transcribed strand which serves as the template for the synthesis of RNA. As indicated in Table 7, this effect was observed over a range of oligonucleotide concentrations from 0-3.6 μ g, although we did observe some variability in the difference between the two oligonucleotides (indicated in Table 7 as a fold difference between HygE3T/74 α and HygE3T/74). Furthermore, as shown in Table 8, we observe increased efficiency of correction by HygE3T/74 α relative to HygE3T/74 regardless of whether the oligonucleotides were used to correct the base substitution

mutation in pAURHYG(rep)GFP or the insertion mutation in pAURHYG(ins)GFP. The data presented in Table 8 further indicate that the single-stranded oligonucleotides correct a base substitution mutation more efficiently than an insertion mutation. However, this last effect was much less pronounced and the oligonucleotides of the invention are clearly able efficiently to correct both types of mutations in yeast cells. In addition, the role of transcription is investigated using plasmids with inducible promoters such as that described in Figure 10.

Optimization of oligonucleotide concentration. To determine the optimal concentration of oligonucleotide for the purpose of gene alteration, we test the ability of increasing concentrations of Hyg3T/74 α to correct the mutation in pAURHYG(rep)GFP contained in yeast LSY678. We chose this assay system because our previous experiments indicated that it supports the highest level of correction. However, this same approach could be used to determine the optimal concentration of any given oligonucleotide. We test the ability of Hyg3T/74 α to correct the mutation in pAURHYG(rep)GFP contained in yeast LSY678 over a range of oligonucleotide concentrations from 0-10.0 μ g. As shown in Table 9, we observe that the correction efficiency initially increases with increasing oligonucleotide concentration, but then declines at the highest concentration tested.

Tables are attached hereto.

Table 6

Correction of an insertion mutation in *pAURHYG(ins)GFP* by *HygGG/Rev*, *HygE3T/25* and *HygE3T/74*

5

Oligonucleotide Tested	Colonies on Hygromycin	Colonies on Aureobasidin (/10 ⁵)	Correction Efficiency
HygGG/Rev	3	157	0.02
HygE3T/25	64	147	0.44
HygE3T/74	280	174	1.61
Kan70T	0	—	—

Table 7

An oligonucleotide targeting the sense strand of the target sequence corrects more efficiently.

10

Amount of Oligonucleotide (μg)	Colonies per hygromycin plate	
	HygE3T/74	HygE3T/74α
0	0	0
0.6	24	128 (8.4x)*
1.2	69	140 (7.5x)*
2.4	62	167 (3.8x)*
3.6	29	367 (15x)*

15

* The numbers in parentheses represent the fold increase in efficiency for targeting the non-transcribed strand as compared to the other strand of a DNA duplex that encodes a protein.

Table 8

Correction of a base substitution mutation is more efficient than correction of a frame shift mutation.

Oligonucleotide Tested (5 µg)	Plasmid tested (contained in LSY678)	
	pAURHYG(ins)GFP	pAURHYG(rep)GFP
HygE3T/74	72	277
HygE3T/74α	1464	2248
Kan70T	0	0

Table 9

Optimization of oligonucleotide concentration in electroporated yeast cells.

Amount (µg)	Colonies on hygromycin	Colonies on aureobasidin (/10 ⁵)	Correction efficiency
0	0	67	0
1.0	5	64	0.08
2.5	47	30	1.57
5.0	199	33	6.08
7.5	383	39	9.79
10.0	191	33	5.79

Example 3 Cultured Cell Manipulation

Mononuclear cells are isolated from human umbilical cord blood of normal donors using Ficoll Hypaque (Pharmacia Biotech, Uppsala, Sweden) density centrifugation. CD34⁺ cells are immunomagnetically purified from mononuclear cells using either the progenitor or Multisort Kits (Milenyi Biotech, Auburn, CA). Lin⁻CD38⁻ cells are purified from the mononuclear cells using negative selection with StemSep system according to the manufacturer's protocol (Stem Cell Technologies, Vancouver, CA).

Cells used for microinjection are either freshly isolated or cryopreserved and cultured in Stem Medium (S Medium) for 2 to 5 days prior to microinjection. S Medium contains Iscoves' Modified Dulbecco's Medium without phenol red (IMDM) with 100 µg/ml glutamine/penicillin/streptomycin, 50 mg/ml bovine serum albumin, 50 µg/ml bovine pancreatic insulin, 1 mg/ml human transferrin, and IMDM; Stem Cell Technologies), 40 µg/ml low-density lipoprotein (LDL; Sigma, St. Louis, MO), 50 mM HEPES buffer and 50 µM 2-mercaptoethanol, 20 ng/ml each of thrombopoietin, flt-3 ligand, stem cell factor and human IL-6 (Pepro Tech Inc., Rocky Hill, NJ). After microinjection, cells are detached and transferred in bulk into wells of 48 well plates for culturing.

35 mm dishes are coated overnight at 4° C with 50 µg/ml Fibronectin (FN) fragment CH-296 (Retronectin; TaKaRa Biomedicals, Panvera, Madison, WI) in phosphate buffered saline and washed with IMDM containing glutamine/penicillin/streptomycin. 300 to 2000 cells are added to cloning rings and attached to the plates for 45 minutes at 37° C prior to microinjection. After incubation, cloning rings are removed and 2 ml of S Medium are added to each dish for microinjection. Pulled injection needles with a range of 0.22 µ to 0.3 µ outer tip diameter are used. Cells are visualized with a microscope equipped with a temperature controlled stage set at 37° C and injected using an electronically interfaced Eppendorf Micromanipulator and Transjector. Successfully injected cells are intact, alive and remain attached to the plate post injection. Molecules that are fluorescently labeled allow determination of the amount of oligonucleotide delivered to the cells.

For in vitro erythropoiesis from Lin⁻CD38⁻ cells, the procedure of Malik, 1998 can be used. Cells are cultured in ME Medium for 4 days and then cultured in E Medium for 3 weeks. Erythropoiesis is evident by glycophorin A expression as well as the presence of red color representing the presence of hemoglobin in the cultured cells. The injected cells are able to retain their proliferative capacity and the ability to generate myeloid and erythroid progeny. CD34⁺ cells can convert a normal A (β^A) to sickle T (β^S) mutation in the β-globin gene or can be altered using any of the oligonucleotides of the invention herein for correction or alteration of a normal gene to a mutant gene. Alternatively, stem cells can be isolated from blood of humans having genetic disease mutations and the oligonucleotides of the invention can be used to correct a defect or to modify genomes within those cells.

Alternatively, non-stem cell populations of cultured cells can be manipulated using any method known to those of skill in the art including, for example, the use of polycations, cationic lipids, liposomes, polyethylenimine (PEI), electroporation, biolistics, calcium phosphate precipitation, or any other method known in the art.

Notes on the tables presented below:

Each of the following tables presents, for the specified human gene, a plurality of mutations that are known to confer a clinically-relevant phenotype and, for each mutation, the oligonucleotides that can be used to correct the respective mutation site-specifically in the human genome according to the present invention.

The left-most column identifies each mutation and the clinical phenotype that the mutation confers.

For most entries, the mutation is identified at both the nucleic acid and protein level. At the amino acid level, mutations are presented according to the following standard nomenclature. The centered number identifies the position of the mutated codon in the protein sequence; to the left of the number is the wild type residue and to the right of the number is the mutant codon. Codon numbering is according to the Human Gene Mutation Database, Cardiff, Wales, UK (<http://archive.uwcm.ac.uk/search/mg/allgenes>). Terminator codons are shown as "TERM". At the nucleic acid level, the entire triplet of the wild type and mutated codons is shown.

The middle column presents, for each mutation, four oligonucleotides capable of repairing the mutation site-specifically in the human genome or in cloned human DNA including human DNA in artificial chromosomes, episomes, plasmids, or other types of vectors. The oligonucleotides of the invention, however, may include any of the oligonucleotides sharing portions of the sequence of the 121 base sequence. Thus, oligonucleotides of the invention for each of the depicted targets may be 18, 19, 20 up to about 121 nucleotides in length. Sequence may be added non-symmetrically.

All oligonucleotides are presented, per convention, in the 5' to 3' orientation. The nucleotide that effects the change in the genome is underlined and presented in bold.

The first of the four oligonucleotides for each mutation is a 121 nt oligonucleotide centered about the repair nucleotide. The second oligonucleotide, its reverse complement, targets the opposite strand of the DNA duplex for repair. The third oligonucleotide is the minimal 17 nt domain of the first oligonucleotide, also centered about the repair nucleotide. The fourth oligonucleotide is the reverse complement of the third, and thus represents the minimal 17 nt domain of the second.

The third column of each table presents the SEQ ID NO: of the respective repair oligonucleotide.

EXAMPLE 4

Adenosine Deaminase (ADA)

Adenosine deaminase (ADA, EC 3.5.4.4) catalyses the deamination of adenosine and 2'-deoxyadenosine to inosine or 2'-deoxyinosine respectively. ADA deficiency has been identified as the metabolic basis for 20-30% of cases with recessively inherited severe combined immunodeficiency (SCID). Affected infants are subject to recurrent chronic viral, fungal, protozoal, and bacterial infections and frequently present with persistent diarrhea, failure to thrive and candidiasis. In patients homozygous for ADA deficiency, 2'-deoxyadenosine accumulating during the rapid turnover of cells rich in DNA is converted back to dATP, either by adenosine kinase or deoxycytidine kinase. Many hypotheses have been advanced to explain the specific toxicity to the immune system in ADA deficiency. The apparently selective accumulation of dATP in thymocytes and peripheral blood B cells, with resultant inhibition of ribonucleotide reductase and DNA synthesis is probably the principal mechanism.

The structural gene for ADA is encoded as a single 32 kb locus containing 12 exons. Studies of the molecular defect in ADA-deficient patients have shown that mRNA is usually detectable in normal or supranormal amounts. Specific base substitution mutations have been detected in the majority of cases with the complete deficiency. A C-to-T base substitution mutation in exon 11 accounts for a high proportion of these, whilst a few patients are homozygous for large deletions encompassing exon 1. A common point mutation resulting in a heat-labile ADA has been characterised in some patients with partial ADA deficiency, a disorder with an apparently increased prevalence in the Caribbean.

As yet no totally effective therapy for ADA deficiency has been reported, except in those few cases where bone marrow from an HLA/MLR compatible sibling donor was available.

Two therapeutic approaches have provided long-term benefit in specific instances. First, reconstitution using T cell depleted mismatched sibling marrow has been encouraging, particularly in early presenters completely deficient in ADA. Secondly, therapy with polyethylene glycol-modified adenosine deaminase (PEG-ADA) for more than 5 years has produced a sustained increase in lymphocyte numbers and mitogen responses together with evidence of in vivo B cell function. Success has generally been achieved in late presenters with residual ADA activity in mononuclear cells.

ADA deficiency has been chosen as the candidate disease for gene replacement therapy and the first human experiment commenced in 1990. The clinical consequences of overexpression of ADA activity - one of the potential hazards of gene implant - are known and take the form of an hereditary haemolytic anaemia associated with a tissue-specific increase in ADA activity. The genetic basis for the

latter autosomal dominant disorder seemingly relates to markedly increased levels of structurally normal ADA mRNA.

Table 10
ADA Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency GLN3TERM CAG to TAG	AGAGACCCACCGAGCGGGCGGAGGGAGCAGCGCCGGGG CGCACGAGGGCACCATGGCCAGACGCCCCGCTTCGACAAG CCCAAAGTGAGCGCGCGGGGGCTCCGGGGACGGGGGTC	1
	GACCCCCGTCCCCGGAGCCCCGCGCGCGCTCACTTTGGG CTTGTCGAAGGCGGGCGTCTGGGCCATGGTGCCCTCGTGCG CCCCGGCGCTGCTCCCTCCGCCGCGCTCGGTGGGTCTCT	2
	CCATGGCCAGACGCCC	3
	GGGCGTCTGGGCCATGG	4
Adenosine deaminase deficiency HIS15ASP CAT to GAT	TATTTGTTCTCTCTCTCCCTTTCTCTCTCTTCCCCCTGCCC CCTTGCAAGTAGAACTGCATGTCCACCTAGACGGATCCATCA AGCCTGAAACCATCTTATACTATGGCAGGTAAGTCC	5
	GGACTTACCTGCCATAGTATAAGATGGTTTCAGGCTTGATGGA TCCGTCTAGGTGGACATGCAGTTCTACCTGCAAGGGGGCAG GGGGAAGAGAGAGAGAAAGGGAGAGAGAGAAACAAATA	6
	TAGAACTGCATGTCCAC	7
	GTGGACATGCAGTTCTA	8
Adenosine deaminase deficiency GLY20ARG GGA to AGA	TCCCTTTCTCTCTCTTCCCCCTGCCCCCTTGCAAGGTAGAA CTGCATGTCCACCTAGACGGATCCATCAAGCCTGAAACCATC TTATACTATGGCAGGTAAGTCCATACAGAAGAGCCCT	9
	AGGGCTCTTCTGTATGGACTTACCTGCCATAGTATAAGATGGT TTCAGGCTTGATGGATCCGTCTAGGTGGACATGCAGTTCTAC CTGCAAGGGGGCAGGGGGAAGAGAGAGAGAAAGGGA	10
	ACCTAGACGGATCCATC	11
	GATGGATCCGTCTAGGT	12
Adenosine deaminase deficiency GLY74CYS GGC to TGC	CCTGGAGCTCCCAAGGGACTTGGGGAAGGTTGTTCCCAACC CCTTTCTTCCCTTCCCAGGGGCTGCCGGGAGGCTATCAAAAG GATCGCCTATGAGTTTGTAGAGATGAAGGCCAAAGAGG	13

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CCTCTTTGGCCTTCATCTCTACAACTCATAGGCGATCCTTTT GATAGCCTCCCGGCAGCCCTGGGAAGGGAAGAAAGGGTT GGGAACAACCTTCCCCAAGTCCCTTGGGAGCTCCAGG	14
	CTATCGCGGGCTGCCGG	15
	CCGGCAGCCCGCGATAG	16
Adenosine Deaminase Deficiency ARG76TRP CGG to TGG	GCTCCCAAGGGACTTGGGGAAGGTTGTTCCCAACCCCTTTCT TCCCTTCCCAGGGGCTGCCGGGAGGCTATCAAAGGATCGC CTATGAGTTTGTAGAGATGAAGGCCAAAGAGGGCGTGG	17
	CCACGCCCTCTTTGGCCTTCATCTCTACAACTCATAGGCGAT CCTTTTGATAGCCTCCCGGCAGCCCTGGGAAGGGAAGAAA GGGGTTGGGAACAACCTTCCCCAAGTCCCTTGGGAGC	18
	GGGGCTGCCGGGAGGCT	19
	AGCCTCCCAGCAGCCCC	20
Adenosine Deaminase Deficiency LYS80ARG AAA to AGA	TTGGGGAAGGTTGTTCCCAACCCCTTTCTTCCCTTCCCAGGG GCTGCCGGGAGGCTATCAAAGGATCGCCTATGAGTTTGTAG AGATGAAGGCCAAAGAGGGCGTGGTGTATGTGGAGGT	21
	ACCTCCACATACACCACGCCCTCTTTGGCCTTCATCTCTACAA ACTCATAGGCGATCCTTTTGATAGCCTCCCGGCAGCCCCTGG GAAGGGAAGAAAGGGGTTGGGAACAACCTTCCCCAA	22
	GGCTATCAAAGGATCG	23
	CGATCCTTTTGATAGCC	24
Adenosine deaminase deficiency ALA83ASP GCC to GAC	GTTGTTCCCAACCCCTTTCTTCCCTTCCCAGGGGCTGCCGGG AGGCTATCAAAGGATCGCCTATGAGTTTGTAGAGATGAAGG CCAAAGAGGGCGTGGTGTATGTGGAGGTGCGGTACAG	25
	CTGTACCGCACCTCCACATACACCACGCCCTCTTTGGCCTTC ATCTCTACAACTCATAGGCGATCCTTTTGATAGCCTCCCGGC AGCCCCTGGGAAGGGAAGAAAGGGGTTGGGAACAAC	26
	AAGGATCGCCTATGAGT	27
	ACTCATAGGCGATCCTT	28
Adenosine deaminase deficiency TYR97CYS TAT to TGT	AGGCTATCAAAGGATCGCCTATGAGTTTGTAGAGATGAAGG CCAAAGAGGGCGTGGTGTATGTGGAGGTGCGGTACAGTCCG CACCTGCTGGCCAACTCCAAAGTGGAGCCAATCCCCTG	29
	CAGGGGATTGGCTCCACTTTGGAGTTGGCCAGCAGGTGCCG ACTGTACCGCACCTCCACATACACCACGCCCTCTTTGGCCTT CATCTCTACAACTCATAGGCGATCCTTTTGATAGCCT	30

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGTGGTGTATGTGGAGG	31
	CCTCCACATACACCACG	32
Adenosine deaminase deficiency ARG101GLN CGG to CAG	GGATCGCCTATGAGTTTGTAGAGATGAAGGCCAAAGAGGGCG TGGTGTATGTGGAGGTGCCGTACAGTCCGCACCTGCTGGCC AACTCCAAAGTGGAGCCAATCCCCTGGAACCAGGCTGA	33
	TCAGCCTGGTTCCAGGGGATTGGCTCCACTTTGGAGTTGGCC AGCAGGTGCGGACTGTACCGCACCTCCACATACACCACGCC CTCTTTGGCCTTCATCTCTACAAACTCATAGGCGATCC	34
	GGAGGTGCCGTACAGTC	35
	GACTGTACCGCACCTCC	36
Adenosine deaminase deficiency ARG101LEU CGG to CTG	GGATCGCCTATGAGTTTGTAGAGATGAAGGCCAAAGAGGGCG TGGTGTATGTGGAGGTGCCGTACAGTCCGCACCTGCTGGCC AACTCCAAAGTGGAGCCAATCCCCTGGAACCAGGCTGA	37
	TCAGCCTGGTTCCAGGGGATTGGCTCCACTTTGGAGTTGGCC AGCAGGTGCGGACTGTACCGCACCTCCACATACACCACGCC CTCTTTGGCCTTCATCTCTACAAACTCATAGGCGATCC	38
	GGAGGTGCCGTACAGTC	39
	GACTGTACCGCACCTCC	40
Adenosine deaminase deficiency ARG101TRP CGG to TGG	AGGATCGCCTATGAGTTTGTAGAGATGAAGGCCAAAGAGGGCG GTGGTGTATGTGGAGGTGCCGTACAGTCCGCACCTGCTGGC CAACTCCAAAGTGGAGCCAATCCCCTGGAACCAGGCTG	41
	CAGCCTGGTTCCAGGGGATTGGCTCCACTTTGGAGTTGGCCA GCAGGTGCGGACTGTACCGCACCTCCACATACACCACGCC TCTTTGGCCTTCATCTCTACAAACTCATAGGCGATCCT	42
	TGGAGGTGCCGTACAGT	43
	ACTGTACCGCACCTCCA	44
Adenosine deaminase deficiency PRO104LEU CCG to CTG	ATGAGTTTGTAGAGATGAAGGCCAAAGAGGGCGTGGTGTATG TGGAGGTGCGGTACAGTCCGCACCTGCTGGCCAACTCCAAA GTGGAGCCAATCCCCTGGAACCAGGCTGAGTGAGTGAT	45
	ATCACTCACTCAGCCTGGTTCCAGGGGATTGGCTCCACTTTG GAGTTGGCCAGCAGGTGCCGACTGTACCGCACCTCCACATA CACCACGCCCTCTTTGGCCTTCATCTCTACAAACTCAT	46
	GTACAGTCCGCACCTGC	47
	GCAGGTGCCGACTGTAC	48

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency LEU106VAL CTG to GTG	TTTGTAGAGATGAAGGCCAAAGAGGGCGTGGTGTATGTGGAG GTGCGGTACAGTCCGCACCTGCTGGCCAACTCCAAAGTGA GCCAATCCCCTGGAACCAGGCTGAGTGAGTGATGGGCC	49
	GGCCCATCACTCACTCAGCCTGGTTCAGGGGATTGGCTCCA CTTTGGAGTTGGCCAGCAGGTGCGGACTGTACCGCACCTCC ACATACACCACGCCCTCTTTGGCCTTCATCTCTACAAA	50
	GTCCGCACCTGCTGGCC	51
	GGCCAGCAGGTGCGGAC	52
Adenosine deaminase deficiency LEU107PRO CTG to CCG	TAGAGATGAAGGCCAAAGAGGGCGTGGTGTATGTGGAGGTG CGGTACAGTCCGCACCTGCTGGCCAACTCCAAAGTGGAGCC AATCCCCTGGAACCAGGCTGAGTGAGTGATGGGCCTGGA	53
	TCCAGGCCCATCACTCACTCAGCCTGGTTCAGGGGATTGGC TCCACTTTGGAGTTGGCCAGCAGGTGCGGACTGTACCGCAC CTCCACATACACCACGCCCTCTTTGGCCTTCATCTCTA	54
	GCACCTGCTGGCCAACT	55
	AGTTGGCCAGCAGGTGC	56
Adenosine deaminase deficiency PRO126GLN CCA to CAA	GCCTTCCTTTTGCCTCAGGCCCATCCCTACTCCTCTCCTCAC ACAGAGGGGACCTCACCCAGACGAGGTGGTGGCCCTAGTG GGCCAGGGCCTGCAGGAGGGGGAGCGAGACTTCGGGGT	57
	ACCCCGAAGTCTCGCTCCCCCTCCTGCAGGCCCTGGCCAC TAGGGCCACCACCTCGTCTGGGGTGAGGTCCCCTCTGTGTG AGGAGAGGAGTAGGGATGGGCCTGAGGCAAAAGGAAGGC	58
	CCTCACCCAGACGAGG	59
	CCTCGTCTGGGGTGAGG	60
Adenosine deaminase deficiency VAL129MET GTG to ATG	TTTGCCTCAGGCCCATCCCTACTCCTCTCCTCACACAGAGGG GACCTCACCCAGACGAGGTGGTGGCCCTAGTGGGCCAGGG CCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCC	61
	GGGCCTTGACCCCGAAGTCTCGCTCCCCCTCCTGCAGGCCC TGGCCCACTAGGGCCACCACCTCGTCTGGGGTGAGGTCCCC TCTGTGTGAGGAGAGGAGTAGGGATGGGCCTGAGGCAAA	62
	CAGACGAGGTGGTGGCC	63
	GGCCACCACCTCGTCTG	64

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency GLY140GLU GGG to GAG	ACAGAGGGGACCTCACCCCAGACGAGGTGGTGGCCCTAGTG GGCCAGGGCCTGCAGGAGGGGGAGCGAGACTTCGGGGTCA AGGCCCGGTCCATCCTGTGCTGCATGCCACCAGCCCCAG	65
	CTGGGCTGGTGGCGCATGCAGCACAGGATGGACCGGGCCTT GACCCCGAAGTCTCGCTCCCCTCCTGCAGGCCCTGGCCCA CTAGGGCCACCACCTCGTCTGGGGTGAGGTCCCCTCTGT	66
	GCAGGAGGGGGAGCGAG	67
	CTCGCTCCCCTCCTGC	68
Adenosine deaminase deficiency ARG142GLN CGA to CAA	GGGACCTCACCCCAGACGAGGTGGTGGCCCTAGTGGGCCAG GGCCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCC GGTCCATCCTGTGCTGCATGCCACCAGCCCAGTGAGTA	69
	TACTACTGGGCTGGTGGCGCATGCAGCACAGGATGGACCG GGCCTTGACCCCGAAGTCTCGCTCCCCCTCCTGCAGGCCCT GGCCCACTAGGGCCACCACCTCGTCTGGGGTGAGGTCCC	70
	GGGGGAGCGAGACTTCG	71
	CGAAGTCTCGCTCCCC	72
Adenosine deaminase deficiency ARG142TERM CGA to TGA	GGGGACCTCACCCCAGACGAGGTGGTGGCCCTAGTGGGCCA GGGCCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCC CGGTCCATCCTGTGCTGCATGCCACCAGCCCAGTGAGT	73
	ACTACTGGGCTGGTGGCGCATGCAGCACAGGATGGACCG GCCTTGACCCCGAAGTCTCGCTCCCCCTCCTGCAGGCCCTG GCCCACTAGGGCCACCACCTCGTCTGGGGTGAGGTCCCC	74
	AGGGGGAGCGAGACTTC	75
	GAAGTCTCGCTCCCCCT	76
Adenosine deaminase deficiency ARG149GLN CGG to CAG	TGGTGGCCCTAGTGGGCCAGGGCCTGCAGGAGGGGGAGCG AGACTTCGGGGTCAAGGCCCGGTCCATCCTGTGCTGCATGC GCCACCAGCCCAGTGAGTAGGATCACCGCCCTGCCAGGG	77
	CCCTGGGCAGGGCGGTGATCCTACTACTGGGCTGGTGGCG CATGCAGCACAGGATGGACCGGGCCTTGACCCCGAAGTCTC GCTCCCCCTCCTGCAGGCCCTGGCCCACTAGGGCCACCA	78
	CAAGGCCCGGTCCATCC	79
	GGATGGACCGGGCCTTG	80

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency ARG149TRP CGG to TGG	GTGGTGGCCCTAGTGGGCCAGGGCCTGCAGGAGGGGGAGC GAGACTTCGGGGTCAAGGCCCGGTCCATCCTGTGCTGCATG CGCCACCAGCCCAGTGAGTAGGATCACCGCCCTGCCCAGG	81
	CCTGGGCAGGGCGGTGATCCTACTCACTGGGCTGGTGGCGC ATGCAGCACAGGATGGACCGGGCCTTGACCCCGAAGTCTCG CTCCCCCTCCTGCAGGCCCTGGCCCACTAGGGCCACCAC	82
	TCAAGGCCCGGTCCATC	83
	GATGGACCGGGCCTTGA	84
Adenosine deaminase deficiency LEU152MET CTG to ATG	CTAGTGGGCCAGGGCCTGCAGGAGGGGGAGCGAGACTTCG GGGTCAAGGCCCGGTCCATCCTGTGCTGCATGCGCCACCAG CCCAGTGAGTAGGATCACCGCCCTGCCCAGGGCCGCCCGT	85
	ACGGGCGGCCCTGGGCAGGGCGGTGATCCTACTCACTGGG CTGGTGGCGCATGCAGCACAGGATGGACCGGGCCTTGACCC CGAAGTCTCGCTCCCCCTCCTGCAGGCCCTGGCCCACTAG	86
	GGTCCATCCTGTGCTGC	87
	GCAGCACAGGATGGACC	88
Adenosine deaminase deficiency ARG156CYS CGC to TGC	GGCCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCCCG GGTCCATCCTGTGCTGCATGCGCCACCAGCCCAGTGAGTAG GATCACCGCCCTGCCCAGGGCCGCCCGTCTCACCTGGCC	89
	GGCCAGGGTGAGACGGGCGGCCCTGGGCAGGGCGGTGATC CTACTCACTGGGCTGGTGGCGCATGCAGCACAGGATGGACC GGGCCTTGACCCCGAAGTCTCGCTCCCCCTCCTGCAGGCC	90
	GCTGCATGCGCCACCAG	91
	CTGGTGGCGCATGCAGC	92
Adenosine deaminase deficiency ARG156HIS CGC to CAC	GCCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCCCG GTCCATCCTGTGCTGCATGCGCCACCAGCCCAGTGAGTAGG ATCACCGCCCTGCCCAGGGCCGCCCGTCTCACCTGGCCC	93
	GGGCCAGGGTGAGACGGGCGGCCCTGGGCAGGGCGGTGAT CCTACTCACTGGGCTGGTGGCGCATGCAGCACAGGATGGAC CGGGCCTTGACCCCGAAGTCTCGCTCCCCCTCCTGCAGGC	94
	CTGCATGCGCCACCAGC	95
	GCTGGTGGCGCATGCAG	96

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency VAL177MET GTG to ATG	CTGCCCACAGACTGGTCCCCCAAGGTGGTGGAGCTGTGTAA GAAGTACCAGCAGCAGACCGTGGTAGCCATTGACCTGGCTG GAGATGAGACCATCCCAGGAAGCAGCCTCTTGCCTGGAC	97
	GTCCAGGCAAGAGGCTGCTTCCTGGGATGGTCTCATCTCCAG CCAGGTCAATGGCTACCA C GGTCTGCTGCTGGTACTTCTTAC ACAGCTCCACCACCTTGGGGGACCAGTCTGTGGGCAG	98
	AGCAGACCGTGGTAGCC	99
	GGCTACCA C GGTCTGCT	100
Adenosine deaminase deficiency ALA179ASP GCC to GAC	CAGACTGGTCCCCCAAGGTGGTGGAGCTGTGTAAGAAGTAC CAGCAGCAGACCGTGGTAG C CATTGACCTGGCTGGAGATGA GACCATCCCAGGAAGCAGCCTCTTGCCTGGACATGTCCA	101
	TGGACATGTCCAGGCAAGAGGCTGCTTCCTGGGATGGTCTCA TCTCCAGCCAGGTCAATGG C TACCACGGTCTGCTGCTGGTAC TTCTTACACAGCTCCACCACCTTGGGGGACCAGTCTG	102
	CGTGGTAG C CATTGACC	103
	GGTCAATGG C TACCAG	104
Adenosine deaminase deficiency GLN199PRO CAG to CCG	CCATTGACCTGGCTGGAGATGAGACCATCCCAGGAAGCAGC CTCTTGCCTGGACATGTCC A GGCCTACCAGGTGGGTCTCTGT GAGAAGGAATGGAGAGGCTGGCCCTGGGTGAGCTTGTCT	105
	AGACAAGCTCACCCAGGGCCAGCCTCTCCATTCTTCTCACA GGACCCACCTGGTAGGCC T GGACATGTCCAGGCAAGAGGCT GCTTCCTGGGATGGTCTCATCTCCAGCCAGGTCAATGG	106
	ACATGTCC A GGCCTACC	107
	GGTAGGCCTGGACATGT	108
Adenosine deaminase deficiency ARG211CYS CGT to TGT	GCTAGGGCACCCATGACCTGGCTCTCCCCCTTCCAGGAGGC TGTGAAGAGCGGCATTAC C GTACTGTCCACGCCGGGGAGG TGGGCTCGGCCGAAGTAGTAAAGAGGTGAGGGCCTGGG	109
	CCCAGGCCCTCACCTCTTTTACTACTTCGGCCGAGCCACCT CCCCGGCGTGGACAGTAC G GTGAATGCCGCTCTTACAGCC TCCTGGAAGGGGGAGAGCCAGGTCATGGGTGCCCTAGC	110
	GCATTCAC C GTACTGTC	111
	GACAGTAC C GTGAATGC	112

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency ARG211HIS CGT to CAT	CTAGGGCACCCATGACCTGGCTCTCCCCCTTCCAGGAGGCT GTGAAGAGCGGCATTACCCGACTGTCCACGCCGGGGAGGT GGGCTCGGCCGAAGTAGTAAAGAGGTGAGGGCCTGGGC	113
	GCCCAGGCCCTCACCTCTTTTACTACTTCGGCCGAGCCCACC TCCCCGGCGTGGACAGTACGGTGAATGCCGCTCTTACAGC CTCCTGGAAGGGGGAGAGCCAGGTCATGGGTGCCCTAG	114
	CATTCACCCGACTGTCC	115
	GGACAGTACGGTGAATG	116
Adenosine deaminase deficiency ALA215THR GCC to ACC	ATGACCTGGCTCTCCCCCTTCCAGGAGGCTGTGAAGAGCGG CATTACCGTACTGTCCACGCCGGGGAGGTGGGCTCGGCCG AAGTAGTAAAGAGGTGAGGGCCTGGGCTGGCCATGGGG	117
	CCCCATGGCCAGCCCAGGCCCTCACCTCTTTTACTACTTCGG CCGAGCCCACCTCCCCGGCGTGGACAGTACGGTGAATGCCG CTCTTACAGCCTCCTGGAAGGGGGAGAGCCAGGTCAT	118
	CTGTCCACGCCGGGGAG	119
	CTCCCCGGCGTGGACAG	120
Adenosine deaminase deficiency GLY216ARG GGG to AGG	ACCTGGCTCTCCCCCTTCCAGGAGGCTGTGAAGAGCGGCAT TCACCGTACTGTCCACGCCGGGGAGGTGGGCTCGGCCGAAG TAGTAAAGAGGTGAGGGCCTGGGCTGGCCATGGGGTCC	121
	GGACCCCATGGCCAGCCCAGGCCCTCACCTCTTTTACTACTT CGGCCGAGCCCACCTCCCCGGCGTGGACAGTACGGTGAATG CCGCTCTTACAGCCTCCTGGAAGGGGGAGAGCCAGGT	122
	TCCACGCCGGGGAGGTG	123
	CACCTCCCCGGCGTGGA	124
Adenosine deaminase deficiency GLU217LYS GAG to AAG	TGGCTCTCCCCCTTCCAGGAGGCTGTGAAGAGCGGCATTCA CCGTACTGTCCACGCCGGGGAGGTGGGCTCGGCCGAAGTAG TAAAGAGGTGAGGGCCTGGGCTGGCCATGGGGTCCCTC	125
	GAGGGACCCCATGGCCAGCCCAGGCCCTCACCTCTTTTACTA CTTCGGCCGAGCCCACCTCCCCGGCGTGGACAGTACGGTGA ATGCCGCTCTTACAGCCTCCTGGAAGGGGGAGAGCCA	126
	ACGCCGGGGAGGTGGGC	127
	GCCCACCTCCCCGGCGT	128

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency THR233ILE ACA to ATA	CTGCCTCCTCCCATACTTGGCTCTATTCTGCTTCTCTACAGGC TGTGGACATACTCAAGACAGAGCGGCTGGGACACGGCTACC ACACCCTGGAAGACCAGGCCCTTTATAACAGGCTGCG	129
	CGCAGCCTGTTATAAAGGGCCTGGTCTTCCAGGGTGTGGTAG CCGTGTCCCAGCCGCTCTGTCTTGAGTATGTCCACAGCCTGT AGAGAAGCAGAATAGAGCCAAGTATGGGAGGAGGCAG	130
	ACTCAAGACAGAGCGGC	131
	GCCGCTCTGTCTTGAGT	132
Adenosine deaminase deficiency ARG253PRO CGG to CCG	CAGAGCGGCTGGGACACGGCTACCACACCCTGGAAGACCAG GCCCTTTATAACAGGCTGCGGCAGGAAAACATGCACTTCGAG GTAAGCGGGCCAGGGAGTGGGGAGGAACCATCCCCGGC	133
	GCCGGGGATGGTTCCTCCCCACTCCCTGGCCCGCTTACCTC GAAGTGCATGTTTTCTGCGCAGCCTGTTATAAAGGGCCTG GTCTTCAGGGTGTGGTAGCCGTGTCCCAGCCGCTCTG	134
	CAGGCTGCGGCAGGAAA	135
	TTTCCTGCGGCAGCCTG	136
Adenosine deaminase deficiency GLN254TERM CAG to TAG	GAGCGGCTGGGACACGGCTACCACACCCTGGAAGACCAGGC CCTTTATAACAGGCTGCGGCAGGAAAACATGCACTTCGAGGT AAGCGGGCCAGGGAGTGGGGAGGAACCATCCCCGGCTG	137
	CAGCCGGGGATGGTTCCTCCCCACTCCCTGGCCCGCTTACC TCGAAGTGCATGTTTTCTGCGCAGCCTGTTATAAAGGGCC TGGTCTTCAGGGTGTGGTAGCCGTGTCCCAGCCGCTC	138
	GGCTGCGGCAGGAAAAC	139
	GTTTTCTGCGCAGCC	140
Adenosine deaminase deficiency PRO274LEU CCG to CTG	CCACACACCTGCTCTTCCAGATCTGCCCCTGGTCCAGCTACC TCACTGGTGCCTGGAAGCCGGACACGGAGCATGCAGTCATT CGGTGAGCTCTGTTCCCCTGGGCCTGTTCAATTTGTT	141
	AACAAAATTGAACAGGCCAGGGGAACAGAGCTCACCGAATG ACTGCATGCTCCGTGTCCGGCTTCCAGGCACCAAGTGAGGTA GCTGGACCAGGGGCAGATCTGGAAGAGCAGGTGTGTGG	142
	CTGGAAGCCGGACACGG	143
	CCGTGTCCGGCTTCCAG	144

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency SER291LEU TCG to TTG	GGAGGCTGATTCTCTCCTCCTCCCTCTTCTGCAGGCTCAAAA ATGACCAGGCTAACTACTCGCTCAACACAGATGACCCGCTCA TCTTCAAGTCCACCCTGGACACTGATTACCAGATGAC	145
	GTCATCTGGTAATCAGTGTCCAGGGTGGACTTGAAGATGAGC GGGTCATCTGTGTTGAGCGAGTAGTTAGCCTGGTCATTTTGA GCCTGCAGAAGAGGGAGGAGGAGAGAATCAGCCTCC	146
	TAACTACTCGCTCAACA	147
	TGTTGAGCGAGTAGTTA	148
Adenosine deaminase deficiency PRO297GLN CCG to CAG	CCTCCCTCTTCTGCAGGCTCAAAAATGACCAGGCTAACTACT CGCTCAACACAGATGACCCGCTCATCTTCAAGTCCACCCTGG ACACTGATTACCAGATGACCAAACGGGACATGGGCTT	149
	AAGCCCATGTCCCGTTTGGTCATCTGGTAATCAGTGTCCAGG GTGGACTTGAAGATGAGCGGGTCATCTGTGTTGAGCGAGTAG TTAGCCTGGTCATTTTGGCCTGCAGAAGAGGGAGG	150
	AGATGACCCGCTCATCT	151
	AGATGAGCGGGTCATCT	152
Adenosine deaminase deficiency LEU304ARG CTG to CGG	AAAATGACCAGGCTAACTACTCGCTCAACACAGATGACCCGC TCATCTTCAAGTCCACCCTGGACACTGATTACCAGATGACCAA ACGGGACATGGGCTTTACTGAAGAGGAGTTTAAAG	153
	CTTTTAACTCCTCTTCAGTAAAGCCCATGTCCCGTTTGGTCA TCTGGTAATCAGTGTCCAGGGTGGACTTGAAGATGAGCGGGT CATCTGTGTTGAGCGAGTAGTTAGCCTGGTCATTTT	154
	GTCCACCCGGGACACTG	155
	CAGTGTCCAGGGTGGAC	156
Adenosine deaminase deficiency ALA329VAL C-to-T at base 1081	GCCTTCTTTGTTCTCTGGTTCCATGTTGTCTGCCATTCTGGCC TTTCCAGAACATCAATGCGGCCAAATCTAGTTTCTCCAGAA GATGAAAAGAGGGAGCTTCTCGACCTGCTCTATAA	157
	TTATAGAGCAGGTGAGAGAAGCTCCCTCTTTTCATCTTCTGGGA GGAAACTAGATTTGGCCGATTGATGTTCTGGAAAGGCCAGA ATGGCAGACAACATGGAACCAGAGAACAAAGAAGGC	158
	CATCAATGCGGCCAAAT	159
	ATTTGGCCGCATTGATG	160

EXAMPLE 5
P53 Mutations

The p53 gene codes for a protein that acts as a transcription factor and serves as a key regulator of the cell cycle. Mutation in this gene is probably the most significant genetic change characterizing the transformation of cells from normalcy to malignancy.

Inactivation of p53 by mutation disrupts the cell cycle which, in turn, sets the stage for tumor formation. Mutations in the p53 gene are among the most commonly diagnosed genetic disorders, occurring in as many as 50% of cancer patients. For some types of cancer, most notably of the breast, lung and colon, p53 mutations are the predominant genetic alternations found thus far. These mutations are associated with genomic instability and thus an increased susceptibility to cancer. Some p53 lesions result in malignancies that are resistant to the most widely used therapeutic regimens and therefore demand more aggressive treatment.

That p53 is associated with different malignant tumors is illustrated in the Li-Fraumeni autosomal dominant hereditary disorder characterized by familial multiple tumors due to mutation in the p53 gene. Affected individuals can develop one or more tumors, including: brain (12%); soft-tissue sarcoma (12%); breast cancer (25%); adrenal tumors (1%); bone cancer (osteosarcoma) (6%); cancer of the lung, prostate, pancreas, and colon as well as lymphoma and melanoma can also occur.

Certain of the most frequently mutated codons are codons 175, 248 and 273, however a variety of oligonucleotides are described below in the attached table.

Table 11
p53 Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
In 2 families with Li-Fraumeni syndrome, there was a C-to-T mutation at the first nucleotide of codon 248 which changed arginine to tryptophan.	GACTGTACCACCATCCACTACAACCTACATGTGTAAACAGTTCCT GCATGGGCGGCATGAACCGGAGGCCCATCCTCACCATCATC AACTGGAAGACTCCAGGTCAGGAGCCACTTGCCACC	161
	GGTGGCAAGTGGCTCCTGACCTGGAGTCTTCCAGTGTGATGA TGGTGAGGATGGGCCTCCGGTTCATGCCGCCCATGCAGGAA CTGTTACACATGTAGTTGTAGTGGATGGTGGTACAGTC	162
	GCATGAACCGGAGGCCC	163

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GGGCCTCC <u>G</u> GTTTCATGC	164
In a family with the Li-Fraumeni syndrome, a G-to-A mutation at the first nucleotide of codon 258 resulting in the substitution of lysine for glutamic acid.	TGTAACAGTTCCTGCATGGGCGGCATGAACCGGAGGCCCAT CCTCACCATCATCACA <u>C</u> TGGAAGACTCCAGGTCAGGAGCCAC TTGCCACCCTGCACA <u>C</u> TGGCCTGCTGTGCCCCAGCCTC	165
	GAGGCTGGGGCACAGCAGGCCAGTGTGCAGGGTGGCAAGT GGCTCCTGACCTGGAGTCTT <u>C</u> CAGTGTGATGATGGTGAGGAT GGGCCTCCGGTTCATGCCGCCCATGCAGGAACTGTTACA	166
	TCACA <u>C</u> TGGAAGACTCC	167
	GGAGTCTT <u>C</u> CAGTGTGA	168
In a family with the Li-Fraumeni syndrome, a G-to-T mutation at the first nucleotide of codon 245 resulting in the substitution of cysteine for glycine.	GTTGGCTCTGACTGTACCACCATCCACTACA <u>A</u> CTACATGTGTA ACAGTTCCTGCATGGGCGGCATGAACCGGAGGCCCATCCTC ACCATCATCACA <u>C</u> TGGAAGACTCCAGGTCAGGAGCCA	169
A gly245-to-ser, GGC-to-AGC, mutation was found in a patient in whom osteosarcoma was diagnosed at the age of 18 years.	TGGCTCCTGACCTGGAGTCTTCCAGTGTGATGATGGTGAGGA TGGGCCTCCGGTTCATGCC <u>G</u> CCCATGCAGGAACTGTTACACA TGTAGTTGTAGTGGATGGTGGTACAGTCAGAGCCAAC	170
	GCATGGGC <u>G</u> GCATGAAC	171
	GTTCATGCC <u>G</u> CCCATGC	172
In a family with the Li-Fraumeni syndrome, a germline mutation at codon 252: a T-to-C change at the second position resulted in substitution of proline for leucine.	TCCACTACA <u>A</u> CTACATGTGTAACAGTTCCTGCATGGGCGGCA TGAACCGGAGGCCCATCCTCACCATCATCACA <u>C</u> TGGAAGACT CCAGGTCAGGAGCCACTTGCCACCCTGCACA <u>C</u> TGGCC	173
	GGCCAGTGTGCAGGGTGGCAAGTGGCTCCTGACCTGGAGTC TTCCAGTGTGATGATGGTG <u>A</u> GGATGGGCCTCCGGTTCATGCC GCCCATGCAGGAACTGTTACACATGTAGTTGTAGTGGA	174
	GCCCATCCTCACCATCA	175
	TGATGGTG <u>A</u> GGATGGGC	176

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
<p>5 10 15 20 25</p> <p>Researchers analyzed for mutations in p53 hepatocellular carcinomas from patients in Qidong, an area of high incidence in China, in which both hepatitis B virus and aflatoxin B1 are risk factors. Eight of 16 tumors had a point mutation at the third base position of codon 249. The G-to-T mutation at codon 249 led to a change from arginine to serine (AGG to AGT).</p>	TACCACCATCCACTACAACATCATGTGTAACAGTTCCTGCATG GGCGGCATGAACCGGAGGCCCATCCTCACCATCATCACACT GGAAGACTCCAGGTGAGGAGCCACTTGCCACCCTGCA	177
	TGCAGGGTGGCAAGTGGCTCCTGACCTGGAGTCTTCCAGTG TGATGATGGTGAAGATGGGCTCCGGTTCATGCCGCCCATG CAGGAAGTGTACACATGTAGTTGTAGTGGATGGTGGTA	178
	AACCGGAGGCCCATCCT	179
	AGGATGGGCTCCGGTT	180
<p>30 35 40</p> <p>In cases of hepatocellular carcinoma in southern Africa, a G-to-T substitution in codon 157 resulting in a change from valine to phenylalanine.</p>	CTGGCCAAGACCTGCCCTGTGCAGCTGTGGGTGATTCCACA CCCCCGCCCGGCACCCGCTCCGCGCCATGGCCATCTACAA GCAGTCACAGCACATGACGGAGGTTGTGAGGCGCTGCC	181
	GGCAGCGCCTCACAACCTCCGTGTCATGTGCTGTGACTGCTTGT AGATGGCCATGGCGCGGACGCGGGTGCCGGGCGGGGGTGT GGAATCAACCCACAGCTGCACAGGGCAGGTCTTGCCAG	182
	GCACCCGCGTCCGCGCC	183
	GGCGCGGACGCGGGTGC	184
<p>30 35 40</p> <p>In a family with Li-Fraumeni in which noncancerous skin fibroblasts from affected individuals showed an unusual radiation-resistant phenotype, a point mutation in codon 245 of the P53 gene. A change from GGC to GAC predicted substitution of aspartic acid for glycine.</p>	TTGGCTCTGACTGTACCACCATCCACTACAACATCATGTGTAA CAGTTCCTGCATGGGCGGCATGAACCGGAGGCCCATCCTCA CCATCATCACACTGGAAGACTCCAGGTCAGGAGCCAC	185
	GTGGCTCCTGACCTGGAGTCTTCCAGTGTGATGATGGTGAGG ATGGGCCTCCGGTTCATGCCGCCCATGCAGGAAGTGTACAC ATGTAGTTGTAGTGGATGGTGGTACAGTCAGAGCCAA	186
	CATGGGCGGCATGAACC	187
	GGTTATGCCGCCCATG	188

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
In 2 of 8 families with Li-Fraumeni syndrome, a mutation in codon 248: a CGG-to-CAG change resulting in substitution of glutamine for arginine.	ACTGTACCACCATCCACTACAACCTACATGTGTAACAGTTCCTG CATGGGCGGCATGAACCGGAGGCCCATCCTCACCATCATCA CACTGGAAGACTCCAGGTCAGGAGCCACTTGCCACCC	189
	GGGTGGCAAGTGGCTCCTGACCTGGAGTCTTCCAGTGTGAT GATGGTGAGGATGGGCCTCCGGTTCATGCCGCCCATGCAGG AACTGTTACACATGTAGTTGTAGTGGATGGTGGTACAGT	190
	CATGAACCGGAGGCCCA	191
	TGGGCCTCCGGTTCATG	192
In 9 members of an extended family with Li-Fraumeni syndrome, a germline mutation at codon 133 (ATG-to-ACG), resulted in the substitution of threonine for methionine (M133T), and completely cosegregated with the cancer syndrome.	CCCTGACTTTCAACTCTGTCTCCTTCCTTCCTACAGTACTC CCCTGCCCTCAACAAGATGTTTTGCCAACTGGCCAAGACCTG CCCTGTGCAGCTGTGGGTTGATTCCACACCCCCGCC	193
	GGCGGGGGTGTGGAATCAACCCACAGCTGCACAGGGCAGGT CTTGCCAGTTGGCAAAACATCTTGTTGAGGGCAGGGGAGTA CTGTAGGAAGAGGAAGGAGACAGAGTTGAAAGTCAGGG	194
	CAACAAGATGTTTTGCC	195
	GGCAAAACATCTTGTTG	196
In 1 pedigree consistent with the Li-Fraumeni syndrome, a germline G-to-T transversion at codon 272 (valine to leucine) was found.	TCTTGCTTCTCTTTTCTATCCTGAGTAGTGGTAATCTACTGG GACGGAACAGCTTTGAGGTGCGTGTTTGTGCCTGTCCTGGGA GAGACCGGCGCACAGAGGAAGAGAATCTCCGCAAGA	197
	TCTTGCGGAGATTCTCTTCTCTGTGCGCCGGTCTCTCCAG GACAGGCACAAACACGCACCTCAAAGCTGTTCCGTCCCAGTA GATTACCACTACTCAGGATAGGAAAAGAGAAGCAAGA	198
	GCTTTGAGGTGCGTGTT	199
	AACACGCACCTCAAAGC	200
A ser241-to-phe mutation due to a TCC-to-TTC change was found in a patient with hepatoblastoma and multiple foci of osteosarcoma.	TTATCTCCTAGGTTGGCTCTGACTGTACCACCATCCACTACAA CTACATGTGTAACAGTTCCTGCATGGGCGGCATGAACCGGAG GCCCATCCTCACCATCATCACTGGAAGACTCCAG	201
	CTGGAGTCTTCCAGTGTGATGATGGTGAGGATGGGCCTCCG GTTTCATGCCGCCCATGCAGGACTGTTACACATGTAGTTGTA GTGGATGGTGGTACAGTCAGAGCCAACCTAGGAGATAA	202

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAACAGTT <u>C</u> CTGCATGG	203
	CCATGCAG <u>G</u> AACTGTTA	204
An AAG-to-TAG change of codon 120, resulting in conversion from lysine to a stop codon, was found in a patient with osteosarcoma and adenocarcinoma of the lung at age 18 and brain tumor (glioma) at the age of 27.	CAGAAAACCTACCAGGGCAGCTACGGTTTCCGTCTGGGCTTC TTGCATTCTGGGACAGCC <u>A</u> AGTCTGTGACTTGACGGTCAGT TGCCCTGAGGGGCTGGCTTCCATGAGACTTCAATGCC	205
	GGCATTGAAGTCTCATGGAAGCCAGCCCCCTCAGGGCAACTG ACCGTGCAAGTCACAGACTTGGCTGTCCCAGAATGCAAGAAG CCCAGACGGAAACCGTAGCTGCCCTGGTAGGTTTTCTG	206
	GGACAGCC <u>A</u> AGTCTGTG	207
	CACAGACTTGGCTGTCC	208
A CGG-to-TGG change at codon 282, resulting in the substitution of tryptophan for arginine, was found in a patient who developed osteosarcoma at the age of 10 years.	GGTAATCTACTGGGACGGAACAGCTTTGAGGTGCGTGTTTGT GCCTGTCTCTGGGAGAGAC <u>C</u> GGCGCACAGAGGAAGAGAATCT CCGCAAGAAAGGGGAGCCTCACCACGAGCTGCCCCCAG	209
	CTGGGGGCAGCTCGTGGTGAGGCTCCCCTTTCTTGCGGAGA TTCTCTTCCTCTGTGCGCC <u>G</u> GTCTCTCCAGGACAGGCACAA ACACGCACCTCAAAGCTGTTCCGTCCCAGTAGATTACC	210
	GGAGAGAC <u>C</u> GGCGCACA	211
	TGTGCGCC <u>G</u> GTCTCTCC	212
In 5 of 6 anaplastic carcinomas of the thyroid and in an anaplastic carcinoma thyroid cell line ARO, a CGT-to-CAT mutation converted arginine-273 to histidine.	GCTTCTCTTTTCCTATCCTGAGTAGTGGTAATCTACTGGGACG GAACAGCTTTGAGGTGCGTGTGTTGTGCCTGTCCTGGGAGAGA CCGGCGCACAGAGGAAGAGAATCTCCGCAAGAAAGG	213
	CCTTTCTTGCGGAGATTCTCTTCCTCTGTGCGCCGGTCTCTC CCAGGACAGGCACAAACA <u>C</u> GCACCTCAAAGCTGTTCCGTCCC AGTAGATTACCACTACTCAGGATAGGAAAAGAGAAGC	214
	TGAGGTGCGTGTGTTGTG	215
	CACAAACA <u>C</u> GCACCTCA	216

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
A germline GGA-to-GTA mutation resulting in a change of glycine-325 to valine was found in a patient who had non-Hodgkin lymphoma diagnosed at age 17 and colon carcinoma at age 26.	TCCTAGCACTGCCCAACAACACCAGCTCCTCTCCCCAGCCAA AGAAGAAACCACTGGATGGAGAATATTTACCCTTCAGGTACT AAGTCTTGGGACCTCTTATCAAGTGGAAGTTTCCA	217
	TGGAACTTTCCACTTGATAAGAGGTCCCAAGACTTAGTACCT GAAGGGTGAAATATTCTCCATCCAGTGGTTTCTTCTTTGGCTG GGGAGAGGAGCTGGTGTGTTGGGCAGTGCTAGGA	218
	ACTGGATGGAGAATATT	219
	AATATTCTCCATCCAGT	220
CGC-CCC Arg-72 to Pro association with Lung cancer	AATGGTTCACTGAAGACCCAGGTCCAGATGAAGCTCCCAGAA TGCCAGAGGCTGCTCCCCGCGTGGCCCCTGCACCAGCAGCT CCTACACCGGCGGCCCTGCACCAGCCCCCTCCTGGCC	221
	GGCCAGGAGGGGGCTGGTGCAGGGGCCGCCGGTGTAGGAG CTGCTGGTGCAGGGGCCACGCGGGGAGCAGCCTCTGGCATT CTGGGAGCTTCATCTGGACCTGGGTCTTCAGTGAACCATT	222
	TGCTCCCCGCGTGGCCC	223
	GGGCCACGCGGGGAGCA	224
CCG-CTG Pro-82 to Leu Breast cancer	AAGCTCCCAGAATGCCAGAGGCTGCTCCCCGCGTGGCCCCT GCACCAGCAGCTCCTACACCGGCGGCCCTGCACCAGCCCC CTCCTGGCCCCTGTCATCTTCTGTCCCTTCCCAGAAAAC	225
	GTTTTCTGGGAAGGGACAGAAGATGACAGGGGCCAGGAGGG GGCTGGTGCAGGGGCCGCCGGTGTAGGAGCTGCTGGTGCA GGGGCCACGCGGGGAGCAGCCTCTGGCATTCTGGGAGCTT	226
	TCCTACACCGGCGGCC	227
	GGGCCGCCGGTGTAGGA	228
cCAA-TAA Gln-136 to Term Li-Fraumeni syndrome	TTCAACTCTGTCTCCTTCTCTCTACAGTACTCCCCTGCCC TCAACAAGATGTTTTGCCAACTGGCCAAGACCTGCCCTGTGC AGCTGTGGGTGATTCCACACCCCCGCCCGGCACCC	229
	GGGTGCCGGGCGGGGGTGTGGAATCAACCCACAGCTGCACA GGGCAGGTCTTGCCAGTTGGCAAAACATCTTGTTGAGGGCA GGGGAGTACTGTAGGAAGAGGAAGGAGACAGAGTTGAA	230
	TGTTTTGCCAACTGGCC	231
	GGCCAGTTGGCAAAACA	232

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
TGC-TAC Cys-141 to Tyr Li-Fraumeni syndrome	TCCTCTTCCTACAGTACTCCCCTGCCCTCAACAAGATGTTTTG CCAACCTGGCCAAGACCTGCCCTGTGCAGCTGTGGGTTGATTC CACACCCCCGCCCCGGCACCCGCGTCCGCGCCATGGC	233
	GCCATGGCGCGGACGCGGGTGCCGGGCGGGGGTGTGGAAT CAACCCACAGCTGCACAGGGCAGGTCTTGCCAGTTGGCAA AACATCTTGTGAGGGCAGGGGAGTACTGTAGGAAGAGGA	234
	CAAGACCTGCCCTGTGC	235
	GCACAGGGCAGGTCTTG	236
aCCC-TCC Pro-151 to Ser Li-Fraumeni syndrome	AACAAGATGTTTTGCCAACTGGCCAAGACCTGCCCTGTGCAG CTGTGGGTTGATTCCACA C CCCCGCCCCGGCACCCGCGTCCG CGCCATGGCCATCTACAAGCAGTCACAGCACATGACGG	237
	CCGTCATGTGCTGTGACTGCTTGTAGATGGCCATGGCGCGG ACGCGGGTGCCGGGCGGGGGTGTGGAATCAACCCACAGCT GCACAGGGCAGGTCTTGCCAGTTGGCAAAACATCTTGT	238
	ATTCCACA C CCCCGCCC	239
	GGGCGGGGGTGTGGAAT	240
CCG-CTG Pro-152 to Leu Adrenocortical carcinoma	AGATGTTTTGCCAACTGGCCAAGACCTGCCCTGTGCAGCTGT GGGTTGATTCCACACCCC G CCCCGGCACCCGCGTCCGCGCC ATGGCCATCTACAAGCAGTCACAGCACATGACGGAGGT	241
	ACCTCCGTCATGTGCTGTGACTGCTTGTAGATGGCCATGGCG CGGACGCGGGTGCCGGGCGGGGGTGTGGAATCAACCCACA GCTGCACAGGGCAGGTCTTGCCAGTTGGCAAAACATCT	242
	CACACCCC C GCCCCGGCA	243
	TGCCGGGCGGGGGTGTG	244
GGC-GTC Gly-154 to Val Glioblastoma	TTTGCCAACCTGGCCAAGACCTGCCCTGTGCAGCTGTGGGTTG ATTCCACACCCCCGCCCC G CACCCGCGTCCGCGCCATGGCC ATCTACAAGCAGTCACAGCACATGACGGAGGTTGTGAG	245
	CTCACAACCTCCGTCATGTGCTGTGACTGCTTGTAGATGGCC ATGGCGCGGACGCGGGTGCCGGGCGGGGGTGTGGAATCAA CCCACAGCTGCACAGGGCAGGTCTTGCCAGTTGGCAA	246
	CCCGCCCC G CACCCGCG	247
	CGCGGGTGCCGGGCGGG	248
CGC-CAC Arg-175 to His Li-Fraumeni syndrome	CCCGCGTCCGCGCCATGGCCATCTACAAGCAGTCACAGCAC ATGACGGAGGTTGTGAGGCG C TGCCCCCACCATGAGCGCTG CTCAGATAGCGATGGTGAGCAGCTGGGGCTGGAGAGACG	249

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGTCTCTCCAGCCCCAGCTGCTCACCATCGCTATCTGAGCAG CGCTCATGGTGGGGGCAGCGCCTCACAACCTCCGTCATGTG CTGTGACTGCTTGTAGATGGCCATGGCGCGGACGCGGG	250
	TGTGAGGCGCTGCCCCC	251
	GGGGGCAGCGCCTCACA	252
tGAG-AAG Glu-180 to Lys Li-Fraumeni syndrome	ATGGCCATCTACAAGCAGTCACAGCACATGACGGAGGTTGTG AGGCGCTGCCCCCACCATGAGCGCTGCTCAGATAGCGATGG TGAGCAGCTGGGGCTGGAGAGACGACAGGGCTGGTTGC	253
	GCAACCAGCCCTGTCGTCTCTCCAGCCCCAGCTGCTCACCAT CGCTATCTGAGCAGCGCTCATGGTGGGGGCAGCGCCTCACA ACCTCCGTCATGTGCTGTGACTGCTTGTAGATGGCCAT	254
	CCCACCATGAGCGCTGC	255
	GCAGCGCTCATGGTGGG	256
gCGC-TGC Arg-181 to Cys Breast cancer	GCCATCTACAAGCAGTCACAGCACATGACGGAGGTTGTGAGG CGCTGCCCCCACCATGAGCGCTGCTCAGATAGCGATGGTGA GCAGCTGGGGCTGGAGAGACGACAGGGCTGGTTGCCA	257
	TGGGCAACCAGCCCTGTCGTCTCTCCAGCCCCAGCTGCTCA CCATCGCTATCTGAGCAGCGCTCATGGTGGGGGCAGCGCCT CACAACCTCCGTCATGTGCTGTGACTGCTTGTAGATGGC	258
	ACCATGAGCGCTGCTCA	259
	TGAGCAGCGCTCATGGT	260
CGC-CAC Arg-81 to His Breast cancer	CCATCTACAAGCAGTCACAGCACATGACGGAGGTTGTGAGGC GCTGCCCCCACCATGAGCGCTGCTCAGATAGCGATGGTGA CAGCTGGGGCTGGAGAGACGACAGGGCTGGTTGCCA	261
	CTGGGCAACCAGCCCTGTCGTCTCTCCAGCCCCAGCTGCTC ACCATCGCTATCTGAGCAGCGCTCATGGTGGGGGCAGCGCC TCACAACCTCCGTCATGTGCTGTGACTGCTTGTAGATGG	262
	CCATGAGCGCTGCTCAG	263
	CTGAGCAGCGCTCATGG	264
CAT-CGT His-193 to Arg Li-Fraumeni syndrome	CCAGGGTCCCCAGGCCTCTGATTCTCACTGATTGCTCTTAG GTCTGGCCCCTCTCAGCATCTTATCCGAGTGAAGGAAATT TGCGTGTGGAGTATTTGGATGACAGAAACACTTTTCG	265
	CGAAAAGTGTTCCTGTCATCCAAATACTCCACACGCAAATTC CTTCCAACCTCGGATAAGATGCTGAGGAGGGGCCAGACCTAAGA GCAATCAGTGAGGAATCAGAGGCCTGGGGACCCTGG	266

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TCCTCAGC <u>A</u> TCTTATCC	267
	GGATAAGAT <u>G</u> CTGAGGA	268
cCGA-TGA Arg-196 to Term Adrenocortical carcinoma	CCCAGGCCCTCTGATTCTCACTGATTGCTCTTAGGTCTGGCC CCTCCTCAGCATCTTATCCGAGTGGAAGGAAATTTGCGTGTG GAGTATTTGGATGACAGAAACACTTTTCGACATAGTG	269
	CACTATGTCGAAAAGTGTTTCTGTCATCCAAATACTCCACACG CAAATTTCTTCCACTCGGATAAGATGCTGAGGAGGGGCCAG ACCTAAGAGCAATCAGTGAGGAATCAGAGGCCTGGG	270
	ATCTTATCCGAGTGGA	271
	TTCCACTCGGATAAGAT	272
cAGA-TGA Arg-209 to Term Li-Fraumeni syndrome	GCCCCTCCTCAGCATCTTATCCGAGTGGAAGGAAATTTGCGT GTGGAGTATTTGGATGACAGAAACACTTTTCGACATAGTGTG GTGGTGCCCTATGAGCCGCCTGAGGTCTGGTTTGCAA	273
	TTGCAAACCAGACCTCAGGCGGCTCATAGGGCACCACCACA CTATGTCGAAAAGTGTTTCTGTCATCCAAATACTCCACACGCA AATTTCTTCCACTCGGATAAGATGCTGAGGAGGGGC	274
	TGGATGACAGAAACACT	275
	AGTGTTTCTGTCATCCA	276
tCGA-TGA Arg-213 to Term Li-Fraumeni syndrome	CATCTTATCCGAGTGGAAGGAAATTTGCGTGTGGAGTATTTG GATGACAGAAACACTTTTCGACATAGTGTGGTGGTGCCCTAT GAGCCGCCTGAGGTCTGGTTTGCAACTGGGGTCTCTG	277
	CAGAGACCCCAGTTGCAAACCAGACCTCAGGCGGCTCATAG GGCACCACCACACTATGTCGAAAAGTGTTTCTGTCATCCAAAT ACTCCACACGCAAATTTCTTCCACTCGGATAAGATG	278
	ACACTTTTCGACATAGT	279
	ACTATGTCGAAAAGTGT	280
gCCC-TCC Pro-219 to Ser Adrenocortical carcinoma	GGAAATTTGCGTGTGGAGTATTTGGATGACAGAAACACTTTTC GACATAGTGTGGTGGTGCCCTATGAGCCGCCTGAGGTCTGG TTTGCAACTGGGGTCTCTGGGAGGAGGGGTTAAGGGT	281
	ACCCTTAACCCCTCCTCCCAGAGACCCCAGTTGCAAACCAGA CCTCAGGCGGCTCATAGGGCACCACCACACTATGTCGAAAAG TGTTTCTGTCATCCAAATACTCCACACGCAAATTTCC	282
	TGGTGGTGCCCTATGAG	283
	CTCATAGGGCACCACCA	284

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
TAT-TGT Tyr-220 to Cys Li-Fraumeni syndrome	ATTTGCGTGTGGAGTATTTGGATGACAGAAACACTTTTCGACA TAGTGTGGTGGTGCCCTATGAGCCGCCTGAGGTCTGGTTTG CAACTGGGGTCTCTGGGAGGAGGGTTAAGGGTGGTT	285
	AACCACCCTTAACCCCTCCTCCCAGAGACCCCAGTTGCAAAC CAGACCTCAGGCGGCTCATAGGGCACCACCACACTATGTCTG AAAAGTGTTTCTGTCATCCAAATACTCCACACGCAAAT	286
	GGTGCCCTATGAGCCGC	287
	GCGGCTCATAGGGCACC	288
cTCT-ACT Ser-227 to Thr Rhabdomyosarcoma	CACAGGTCTCCCCAAGGCGCACTGGCCTCATCTTGGGCCTG TGTTATCTCCTAGGTTGGCTCTGACTGTACCACCATCCACTAC AACTACATGTGTAACAGTTCCTGCATGGGCGGCATGA	289
	TCATGCCGCCCATGCAGGAAGTGTACACATGTAGTTGTAGT GGATGGTGGTACAGTCAGAGCCAACCTAGGAGATAACACAG GCCCAAGATGAGGCCAGTGCGCCTTGGGGAGACCTGTG	290
	AGGTTGGCTCTGACTGT	291
	ACAGTCAGAGCCAACCT	292
cCAC-AAC His-233 to Asn Glioma	GCACTGGCCTCATCTTGGGCCTGTGTTATCTCCTAGGTTGGC TCTGACTGTACCACCATCCACTACAACATACATGTGTAACAGTT CCTGCATGGGCGGCATGAACCGGAGGCCCATCCTCA	293
	TGAGGATGGGCCTCCGGTTCATGCCGCCCATGCAGGAAGTGT TTACACATGTAGTTGTAGTGATGGTGGTACAGTCAGAGCCA ACCTAGGAGATAACACAGGCCCAAGATGAGGCCAGTGC	294
	CCACCATCCACTACAAC	295
	GTTGTAGTGGATGGTGG	296
cAAC-GAC Asn-235 to Asp Adrenocortical carcinoma	GCCTCATCTTGGGCCTGTGTTATCTCCTAGGTTGGCTCTGAC TGTACCACCATCCACTACAACATACATGTGTAACAGTTCCTGCA TGGGCGGCATGAACCGGAGGCCCATCCTCACCATCA	297
	TGATGGTGAGGATGGGCCTCCGGTTCATGCCGCCCATGCAG GAAGTGTACACATGTAGTGTAGTGGATGGTGGTACAGTCA GAGCCAACCTAGGAGATAACACAGGCCCAAGATGAGGC	298
	TCCACTACAACATACATG	299
	CATGTAGTGTAGTGGA	300
AAC-AGC Asn-235 to Ser Rhabdomyosarcoma	CCTCATCTTGGGCCTGTGTTATCTCCTAGGTTGGCTCTGACT GTACCACCATCCACTACAACATACATGTGTAACAGTTCCTGCAT GGGCGGCATGAACCGGAGGCCCATCCTCACCATCAT	301

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGATGGTGAGGATGGGCCTCCGGTTCATGCCGCCCATGCA GGAACGTGTTACACATGTAGTTGTAGTGGATGGTGGTACAGTC AGAGCCAACCTAGGAGATAACACAGGCCCAAGATGAGG	302
	CCACTACA <u>A</u> CTACATGT	303
	ACATGTAGTTGTAGTGG	304
ATCc-ATG Ile-251 to Met Glioma	CATCCACTACA <u>A</u> CTACATGTGTAACAGTTCCTGCATGGGCGG CATGAACCGGAGGCCCAT <u>C</u> CTCACCATCATCACACTGGAAGA CTCCAGGTGAGGAGCCACTTGCCACCCTGCACACTGG	305
	CCAGTGTGCAGGGTGGCAAGTGGCTCCTGACCTGGAGTCTT CCAGTGTGATGATGGTGAG <u>G</u> ATGGGCCTCCGGTTCATGCCG CCCATGCAGGAACTGTTACACATGTAGTTGTAGTGGATG	306
	AGGCCCAT <u>C</u> CTCACCAT	307
	ATGGTGAG <u>G</u> ATGGGCCT	308
ACA-ATA Thr-256 to Ile Glioblastoma	ACATGTGTAACAGTTCCTGCATGGGCGGCATGAACCGGAGG CCCATCCTCACCATCATCA <u>C</u> ACTGGAAGACTCCAGGTCAGGA GCCACTTGCCACCCTGCACACTGGCCTGCTGTGCCCA	309
	TGGGGCACAGCAGGCCAGTGTGCAGGGTGGCAAGTGGCTCC TGACCTGGAGTCTTCCAGT <u>G</u> TGATGATGGTGAGGATGGGCCT CCGGTTCATGCCGCCCATGCAGGAACTGTTACACATGT	310
	CATCATCA <u>C</u> ACTGGAAG	311
	CTTCCAGT <u>G</u> TGATGATG	312
CTG-CAG Leu-257 to Gln Li-Fraumeni syndrome	TGTGTAACAGTTCCTGCATGGGCGGCATGAACCGGAGGCC ATCCTCACCATCATCACACT <u>G</u> GGAAGACTCCAGGTCAGGAGCC ACTTGCCACCCTGCACACTGGCCTGCTGTGCCCCAGCC	313
	GGCTGGGGCACAGCAGGCCAGTGTGCAGGGTGGCAAGTGG CTCCTGACCTGGAGTCTTCC <u>A</u> GTGTGATGATGGTGAGGATGG GCCTCCGGTTCATGCCGCCCATGCAGGAACTGTTACACA	314
	CATCACACT <u>G</u> GGAAGACT	315
	AGTCTTCC <u>A</u> GTGTGATG	316
CTG-CCG Leu-265 to Pro Li-Fraumeni syndrome	GACCTGATTTCTTACTGCCTCTTGCTTCTCTTTTCTATCCT GAGTAGTGGAATCTACT <u>T</u> GGGACGGAACAGCTTTGAGGTGCG TGTTTGTGCCTGTCCTGGGAGAGACCGGCGCACAGA	317
	TCTGTGCGCCGGTCTCTCCAGGACAGGCACAAACACGCAC CTCAAAGCTGTTCCGTCCC <u>A</u> GTAGATTACCACTACTCAGGAT AGGAAAAGAGAAGCAAGAGGCAGTAAGGAAATCAGGTC	318

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAATCTACTGGGACGGA	319
	TCCGTCCCAGTAGATTA	320
gCGT-TGT Arg-273 to Cys Li-Fraumeni syndrome	TGCTTCTCTTTTCCTATCCTGAGTAGTGGTAATCTACTGGGAC GGAACAGCTTTGAGGTGCGTGTTTGTGCCTGTCCTGGGAGA GACCGGCGCACAGAGGAAGAGAATCTCCGCAAGAAAG	321
	CTTTCTTGCGGAGATTCTCTTCTCTGTGCGCCGGTCTCTCC CAGGACAGGCACAAACACGCACCTCAAAGCTGTTCCGTCCCA GTAGATTACCACTACTCAGGATAGGAAAAGAGAAGCA	322
	TTGAGGTGCGTGTTTGT	323
	ACAAACACGCACCTCAA	324
TGT-TAT Cys-275 to Tyr Li-Fraumeni syndrome	CTTTTCCTATCCTGAGTAGTGGTAATCTACTGGGACGGAACA GCTTTGAGGTGCGTGTTTGTGCCTGTCCTGGGAGAGACCGG CGCACAGAGGAAGAGAATCTCCGCAAGAAAGGGGAGCC	325
	GGCTCCCTTTCTTGCGGAGATTCTTCTCTGTGCGCCGG TCTCTCCAGGACAGGCACAAACACGCACCTCAAAGCTGTTT CGTCCCAGTAGATTACCACTACTCAGGATAGGAAAAG	326
	GCGTGTTTGTGCCTGTC	327
	GACAGGCACAAACACGC	328
CCT-CTT Pro-278 to Leu Breast cancer	TCCTGAGTAGTGGTAATCTACTGGGACGGAACAGCTTTGAGG TGCGTGTTTGTGCCTGTCCTGGGAGAGACCGGCGCACAGAG GAAGAGAATCTCCGCAAGAAAGGGGAGCCTCACCACGA	329
	TCGTGGTGAGGCTCCCCTTTCTTGCGGAGATTCTTCTCTCT GTGCGCCGGTCTCTCCAGGACAGGCACAAACACGCACCTC AAAGCTGTTCCGTCCCAGTAGATTACCACTACTCAGGA	330
	TGCCTGTCTGGGAGAG	331
	CTCTCCCAGGACAGGCA	332
AGA-AAA Arg-280 to Lys Glioma	GTAGTGGTAATCTACTGGGACGGAACAGCTTTGAGGTGCGTG TTTGTGCCTGTCCTGGGAGAGACCGGCGCACAGAGGAAGAG AATCTCCGCAAGAAAGGGGAGCCTCACCACGAGCTGCC	333
	GGCAGCTCGTGGTGAGGCTCCCCTTTCTTGCGGAGATTCTCT TCCTCTGTGCGCCGGTCTCTCCAGGACAGGCACAAACACG CACCTCAAAGCTGTTCCGTCCCAGTAGATTACCACTAC	334
	TCCTGGGAGAGACCGGC	335
	GCCGGTCTCTCCAGGA	336

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
GAA-GCA Glu-286 to Ala Adrenocortical carcinoma	GGAACAGCTTTGAGGTGCGTGTTTGTGCCTGTCCTGGGAGA GACCGGCGCACAGAGGAAGAAGAATCTCCGCAAGAAAGGGGA GCCTCACCACGAGCTGCCCCAGGGAGCACTAAGCGAGG	337
	CCTCGCTTAGTGCTCCCTGGGGGCAGCTCGTGGTGAGGCTC CCCTTTCTTGCGGAGATTCTTCTCTGTGCGCCGGTCTCT CCCAGGACAGGCACAAACACGCACCTCAAAGCTGTTCC	338
	AGAGGAAGAAGAATCTCC	339
	GGAGATTCTTCTCTCT	340
CGA-CCA Arg-306 to Pro Rhabdomyosarcoma	AAGAGAATCTCCGCAAGAAAGGGGAGCCTCACCACGAGCTG CCCCCAGGGAGCACTAAGCGAGGTAAGCAAGCAGGACAAGA AGCGGTGGAGGAGACCAAGGGTGCAGTTATGCCTCAGAT	341
	ATCTGAGGCATAACTGCACCCTTGGTCTCCTCCACCGCTTCT TGTCCTGCTTGCTTACCTCGCTTAGTGCTCCCTGGGGGCAGC TCGTGGTGAGGCTCCCCTTTCTTGCGGAGATTCTCT	342
	CACTAAGCGAGGTAAGC	343
	GCTTACCTCGCTTAGTG	344
gCGA-TGA Arg-306 to Term Li-Fraumeni syndrome	GAAGAGAATCTCCGCAAGAAAGGGGAGCCTCACCACGAGCT GCCCCCAGGGAGCACTAAGCGAGGTAAGCAAGCAGGACAAG AAGCGGTGGAGGAGACCAAGGGTGCAGTTATGCCTCAGA	345
	TCTGAGGCATAACTGCACCCTTGGTCTCCTCCACCGCTTCT GTCCTGCTTGCTTACCTCGCTTAGTGCTCCCTGGGGGCAGCT CGTGGTGAGGCTCCCCTTTCTTGCGGAGATTCTCTC	346
	GCACTAAGCGAGGTAAG	347
	CTTACCTCGCTTAGTG	348
gCGC-TGC Arg-337 to Cys Osteosarcoma	GGTACTGTGAATATACTTACTTCTCCCCCTCCTCTGTTGCTGC AGATCCGTGGGCGTGAGCGCTTCGAGATGTTCCGAGAGCTG AATGAGGCCTTGGAAGTCAAGGATGCCAGGCTGGGA	349
	TCCCAGCCTGGGCATCCTTGAGTTCCAAGGCCTCATTGAGCT CTCGGAACATCTCGAAGCGCTCACGCCACGGATCTGCAGC AACAGAGGAGGGGGAGAAGTAAGTATATTCACAGTACC	350
	GGCGTGAGCGCTTCGAG	351
	CTCGAAGCGCTCACGCC	352
CTG-CCG Leu-344 to Pro Li-Fraumeni syndrome	CTCCCCCTCCTCTGTTGCTGCAGATCCGTGGGCGTGAGCGC TTCGAGATGTTCCGAGAGCTGAATGAGGCCTTGGAAGTCAAG GATGCCAGGCTGGGAAGGAGCCAGGGGGGAGCAGGGC	353

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCCCTGCTCCCCCTGGCTCCTTCCCAGCCTGGGCATCCTT GAGTTCCAAGGCCTCATTCAAGCTCTCGGAACATCTCGAAGCG CTCACGCCACGGATCTGCAGCAACAGAGGAGGGGGAG	354
	CCGAGAGCTGAATGAGG	355
	CCTCATTCAAGCTCTCGG	356

EXAMPLE 6 beta globin

Hemoglobin, the major protein in the red blood cell, binds oxygen reversibly and is responsible for the cells' capacity to transport oxygen to the tissues. In adults, the major hemoglobin is hemoglobin A, a tetrameric protein consisting of two identical alpha globin chains and two beta globin chains. Disorders involving hemoglobin are among the most common genetic disorders worldwide, with approximately 5% of the world's population being carriers for clinically important hemoglobin mutations. Approximately 300,000 severely affected homozygotes or compound heterozygotes are born each year.

Mutation of the glutamic acid at position 7 in beta globin to valine causes sickle cell anemia, the clinical manifestations of which are well known. Mutations that cause absence of beta chain cause beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. For clinical purposes, beta-thalassemia is divided into thalassemia major (transfusion dependent), thalassemia intermedia (of intermediate severity), and thalassemia minor (asymptomatic). Patients with thalassemia major present in the first year of life with severe anemia; they are unable to maintain a hemoglobin level about 5 gm/dl.

The beta-thalassemias were among the first human genetic diseases to be examined by means of recombinant DNA analysis. Baysal et al., *Hemoglobin* 19(3-4):213-36 (1995) and others provide a compendium of mutations that result in beta-thalassemia.

Hemoglobin disorders were among the first to be considered for gene therapy. Transcriptional silencing of genes transferred into hematopoietic stem cells, however, poses one of the most significant challenges to its success. If the transferred gene is not completely silenced, a progressive decline in gene expression is often observed. Position effect variegation (PEV) and silencing mechanisms may act on a transferred globin gene residing in chromatin outside of the normal globin locus during the important terminal phases of erythroblast development when globin transcripts normally

accumulate rapidly despite heterochromatization and shutdown of the rest of the genome. The attached table discloses the correcting oligonucleotide base sequences for the beta globin oligonucleotides of the invention.

Table 12
Beta Globin Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Sickle Cell Anemia GLU-7-VAL GAG to GTG	TCTGACACAACCTGTGTTCACTAGCAACCTCAAACAGACACCA TGGTGCACCTGACTCCTGAGGAGAAGTCTGCCGTTACTGCC CTGTGGGGCAAGGTGAACGTGGATGAAGTTGGTGGTGA	357
	TCACCACCAACTTCATCCACGTTACCTTGCCCCACAGGGCA GTAACGGCAGACTTCTCCTCAGGAGTCAGGTGCACCATGGT GTCTGTTTGAGGTTGCTAGTGAACACAGTTGTGTCAGA	358
	GACTCCTGAGGAGAAGT	359
	ACTTCTCCTCAGGAGTC	360
Thalassaemia Beta MET-0-ARG ATG to AGG	CTATTGCTTACATTTGCTTCTGACACAACCTGTGTTCACTAGCA ACCTCAAACAGACACCATGGTGCACCTGACTCCTGAGGAGA AGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	361
	ACGTTACCTTGCCCCACAGGGCAGTAACGGCAGACTTCTC CTCAGGAGTCAGGTGCACCATGGTGTCTGTTTGAGGTTGCT AGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATAG	362
	AGACACCATGGTGCACC	363
	GGTGCACCATGGTGTCT	364
Thalassaemia Beta MET-0-ILE ATG to ATA	TATTGCTTACATTTGCTTCTGACACAACCTGTGTTCACTAGCAA CCTCAAACAGACACCATGGTGCACCTGACTCCTGAGGAGAA GTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTG	365
	CACGTTACCTTGCCCCACAGGGCAGTAACGGCAGACTTCT CCTCAGGAGTCAGGTGCACCATGGTGTCTGTTTGAGGTTGC TAGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATA	366
	GACACCATGGTGCACCT	367
	AGGTGCACCATGGTGTCT	368
Thalassaemia Beta MET-0-ILE ATG to ATT	TATTGCTTACATTTGCTTCTGACACAACCTGTGTTCACTAGCAA CCTCAAACAGACACCATGGTGCACCTGACTCCTGAGGAGAA GTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTG	369

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CACGTTACCTTGCCCCACAGGGCAGTAACGGCAGACTTCT CCTCAGGAGTCAGGTGCACCATGGTGTCTGTTTGAGGTTGC TAGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATA	370
	GACACCATGGTGCACCT	371
	AGGTGCACCATGGTGTCT	372
Thalassaemia Beta MET-0-LYS ATG to AAG	CTATTGCTTACATTTGCTTCTGACACAACCTGTGTTCACTAGCA ACCTCAAACAGACACCATGGTGCACCTGACTCCTGAGGAGA AGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	373
	ACGTTACCTTGCCCCACAGGGCAGTAACGGCAGACTTCTC CTCAGGAGTCAGGTGCACCATGGTGTCTGTTTGAGGTTGCT AGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATAG	374
	AGACACCATGGTGCACCT	375
	GGTGCACCATGGTGTCT	376
Thalassaemia Beta MET-0-THR ATG to ACG	CTATTGCTTACATTTGCTTCTGACACAACCTGTGTTCACTAGCA ACCTCAAACAGACACCATGGTGCACCTGACTCCTGAGGAGA AGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	377
	ACGTTACCTTGCCCCACAGGGCAGTAACGGCAGACTTCTC CTCAGGAGTCAGGTGCACCATGGTGTCTGTTTGAGGTTGCT AGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATAG	378
	AGACACCATGGTGCACCT	379
	GGTGCACCATGGTGTCT	380
Thalassaemia Beta MET-0-VAL ATG to GTG	TCTATTGCTTACATTTGCTTCTGACACAACCTGTGTTCACTAGC AACCTCAAACAGACACCATGGTGCACCTGACTCCTGAGGAG AAGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACG	381
	CGTTACCTTGCCCCACAGGGCAGTAACGGCAGACTTCTCC TCAGGAGTCAGGTGCACCATGGTGTCTGTTTGAGGTTGCTAG TGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATAGA	382
	CAGACACCATGGTGCAC	383
	GTGCACCATGGTGTCTG	384
Thalassaemia Beta TRP-16-Term TGG to TGA	TCAAACAGACACCATGGTGCACCTGACTCCTGAGGAGAAGT CTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGAA GTTGGTGGTGAAGGCCCTGGGCAGGTTGGTATCAAGGTTA	385
	TAACCTTGATACCAACCTGCCAGGGCCTCACCACCAACTTC ATCCACGTTACCTTGCCACAGGGCAGTAACGGCAGACT TCTCCTCAGGAGTCAGGTGCACCATGGTGTCTGTTTGA	386

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCCCTGTGGGGCAAGGT	387
	ACCTTGCCCCACAGGGC	388
Thalassaemia Beta TRP-16-Term TGG to TAG	CTCAAACAGACACCATGGTGCACCTGACTCCTGAGGAGAAG TCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGA AGTTGGTGGTGAAGGCCCTGGGCAGGTTGGTATCAAGGTT	389
	AACCTTGATACCAACCTGCCCAGGGCCTCACCACCAACTTCA TCCACGTTACCTTGCCCCACAGGGCAGTAACGGCAGACTT CTCCTCAGGAGTCAGGTGCACCATGGTGTCTGTTTGAG	390
	TGCCCTGTGGGGCAAGG	391
	CCTTGCCCCACAGGGCA	392
Thalassaemia Beta LYS-18-Term AAG to TAG	ACAGACACCATGGTGCACCTGACTCCTGAGGAGAAGTCTGC CGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGAAGTTG GTGGTGAAGGCCCTGGGCAGGTTGGTATCAAGGTTACAAG	393
	CTTGTAACCTTGATACCAACCTGCCCAGGGCCTCACCACCAA CTTCATCCACGTTACCTTGCCCCACAGGGCAGTAACGGCA GACTTCTCCTCAGGAGTCAGGTGCACCATGGTGTCTGT	394
	TGTGGGGCAAGGTGAAC	395
	GTTACCTTGCCCCACA	396
Thalassaemia Beta ASN-20-SER AAC to AGC	CCATGGTGCACCTGACTCCTGAGGAGAAGTCTGCCGTTACT GCCCTGTGGGGCAAGGTGAACGTGGATGAAGTTGGTGGTGA GGCCCTGGGCAGGTTGGTATCAAGGTTACAAGACAGGTT	397
	AACCTGTCTTGTAACCTTGATACCAACCTGCCCAGGGCCTCA CCACCAACTTCATCCACGTTACCTTGCCCCACAGGGCAGTA ACGGCAGACTTCTCCTCAGGAGTCAGGTGCACCATGG	398
	CAAGGTGAACGTGGATG	399
	CATCCACGTTACCTTG	400
Thalassaemia Beta GLU-23-ALA GAA to GCA	ACCTGACTCCTGAGGAGAAGTCTGCCGTTACTGCCCTGTGG GGCAAGGTGAACGTGGATGAAGTTGGTGGTGAAGGCCCTGG GCAGGTTGGTATCAAGGTTACAAGACAGGTTTAAGGAGAC	401
	GTCTCCTTAAACCTGTCTTGTAACCTTGATACCAACCTGCCC AGGGCCTCACCACCAACTTCATCCACGTTACCTTGCCCCAC AGGGCAGTAACGGCAGACTTCTCCTCAGGAGTCAGGT	402
	CGTGGATGAAGTTGGTG	403
	CACCAACTTCATCCAG	404

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Thalassaemia Beta GLU-23-term GAA to TAA	CACCTGACTCCTGAGGAGAAGTCTGCCGTTACTGCCCTGTG GGGCAAGGTGAACGTGGATGAAGTTGGTGGTGAGGCCCTG GGCAGGTTGGTATCAAGGTTACAAGACAGGTTTAAGGAGA	405
	TCTCCTTAAACCTGTCTTGTAACCTTGATACCAACCTGCCCA GGGCCTCACCACCAACTTCATCCACGTTACCTTGCCCCACA GGGCAGTAACGGCAGACTTCTCCTCAGGAGTCAGGTG	406
	ACGTGGATGAAGTTGGT	407
	ACCAACTTCATCCACGT	408
Thalassaemia Beta GLU-27-LYS GAG to AAG	GAGGAGAAGACTGCTGTCAATGCCCTGTGGGGCAAAGTGAA CGTGGATGCAGTTGGTGGTGAGGCCCTGGGCAGGTTGGTAT CAAGGTTATAAGAGAGGCTCAAGGAGGCAAATGGAACT	409
	AGTTTCCATTTGCCTCCTTGAGCCTCTCTTATAACCTTGATAC CAACCTGCCCAGGGCCTCACCACCAACTGCATCCACGTTCA CTTTGCCCCACAGGGCATTGACAGCAGTCTTCTCCTC	410
	TTGGTGGTGAGGCCCTG	411
	CAGGGCCTCACCACCAA	412
Thalassaemia Beta GLU-27-Term GAG to TAG	GAGGAGAAGACTGCTGTCAATGCCCTGTGGGGCAAAGTGAA CGTGGATGCAGTTGGTGGTGAGGCCCTGGGCAGGTTGGTAT CAAGGTTATAAGAGAGGCTCAAGGAGGCAAATGGAACT	413
	AGTTTCCATTTGCCTCCTTGAGCCTCTCTTATAACCTTGATAC CAACCTGCCCAGGGCCTCACCACCAACTGCATCCACGTTCA CTTTGCCCCACAGGGCATTGACAGCAGTCTTCTCCTC	414
	TTGGTGGTGAGGCCCTG	415
	CAGGGCCTCACCACCAA	416
Thalassaemia Beta ALA-28-SER GCC to TCC	GAGAAGACTGCTGTCAATGCCCTGTGGGGCAAAGTGAACGT GGATGCAGTTGGTGGTGAGGCCCTGGGCAGGTTGGTATCAA GGTTATAAGAGAGGCTCAAGGAGGCAAATGGAACTGGG	417
	CCCAGTTTCCATTTGCCTCCTTGAGCCTCTCTTATAACCTTGA TACCAACCTGCCCAGGGCCTCACCACCAACTGCATCCACGT TCACTTTGCCCCACAGGGCATTGACAGCAGTCTTCTC	418
	GTGGTGAGGCCCTGGGC	419
	GCCCAGGGCCTCACCAC	420

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Thalassaemia Beta ARG-31-THR AGG to ACG	CTGTCAATGCCCTGTGGGGCAAAGTGAACGTGGATGCAGTT GGTGGTGAGGCCCTGGGCAGGTTGGTATCAAGGTTATAAGA GAGGCTCAAGGAGGCAAATGGAACTGGGCATGTGTAGA	421
	TCTACACATGCCCAGTTTCCATTTGCCTCCTTGAGCCTCTCTT ATAACCTTGATACCAACCTGCCCAGGGCCTCACCACCAACTG CATCCACGTTCACTTTGCCCCACAGGGCATTGACAG	422
	CCTGGGCAGGTTGGTAT	423
	ATACCAACCTGCCCAGG	424
Thalassaemia Beta Leu-33-GLN CTG to CAG	TGGGTTTCTGATAGGCACTGACTCTCTGTCCCTTGGGCTGTT TTCCTACCCTCAGATTACTGGTGGTCTACCCTTGGACCCAGA GGTCTTTGAGTCCTTTGGGGATCTGTCCTCTCCTGA	425
	TCAGGAGAGGACAGATCCCCAAAGGACTCAAAGAACCTCTG GGTCCAAGGGTAGACCACCAAGTAATCTGAGGGTAGGAAAAC AGCCCAAGGGACAGAGAGTCAGTGCCTATCAGAAACCCA	426
	CAGATTACTGGTGGTCT	427
	AGACCACCAAGTAATCTG	428
Thalassaemia Beta TYR-36-Term TAC to TAA	ATAGGCACTGACTCTCTGTCCCTTGGGCTGTTTTCTACCCT CAGATTACTGGTGGTCTACCCTTGGACCCAGAGGTTCTTTGA GTCCTTTGGGGATCTGTCCTCTCCTGATGCTGTTATG	429
	CATAACAGCATCAGGAGAGGACAGATCCCCAAAGGACTCAA GAACCTCTGGGTCCAAGGGTAGACCACCAAGTAATCTGAGGG TAGGAAAACAGCCCAAGGGACAGAGAGTCAGTGCCTAT	430
	GTGGTCTACCCTTGGAC	431
	GTCCAAGGGTAGACCAC	432
Thalassaemia Beta TRP-38-Term TGG to TGA	ACTGACTCTCTGTCCCTTGGGCTGTTTTCTACCCTCAGATT ACTGGTGGTCTACCCTTGGACCCAGAGGTTCTTTGAGTCCTT TGGGGATCTGTCCTCTCCTGATGCTGTTATGGGCAAC	433
	GTTGCCCATAAACAGCATCAGGAGAGGACAGATCCCCAAAGG ACTCAAAGAACCTCTGGGTCCAAGGGTAGACCACCAAGTAATC TGAGGGTAGGAAAACAGCCCAAGGGACAGAGAGTCAGT	434
	TACCCTTGGACCCAGAG	435
	CTCTGGGTCCAAGGGTA	436
Thalassaemia Beta TRP-38-Term TGG to TAG	CACTGACTCTCTGTCCCTTGGGCTGTTTTCTACCCTCAGAT TACTGGTGGTCTACCCTTGGACCCAGAGGTTCTTTGAGTCCT TTGGGGATCTGTCCTCTCCTGATGCTGTTATGGGCAA	437

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTGCCATAACAGCATCAGGAGAGGACAGATCCCCAAAGGA CTCAAAGAACCTCTGGGTCCAAGGGTAGACCACCAGTAATCT GAGGGTAGGAAAACAGCCCAAGGGACAGAGAGTCAGTG	438
	CTACCCTTGACCCAGA	439
	TCTGGGTCCAAGGGTAG	440
Thalassaemia Beta GLN-40-Term CAG-TAG	ACTCTCTGTCCCTTGGGCTGTTTTCTACCCTCAGATTACTG GTGGTCTACCCTTGGACCCAGAGGTTCTTTGAGTCCTTTGGG GATCTGTCTCTCCTGATGCTGTTATGGGCAACCCTA	441
	TAGGGTTGCCATAACAGCATCAGGAGAGGACAGATCCCCA AAGGACTCAAAGAACCTCTGGGTCCAAGGGTAGACCACCAG TAATCTGAGGGTAGGAAAACAGCCCAAGGGACAGAGAGT	442
	CTTGGACCCAGAGGTTT	443
	GAACCTCTGGGTCCAAG	444
Thalassaemia Beta GLU-44-Term GAG to TAG	TTGGGCTGTTTTCTACCCTCAGATTACTGGTGGTCTACCCT TGGACCCAGAGGTTCTTTGAGTCCTTTGGGGATCTGTCCTCT CCTGATGCTGTTATGGGCAACCCTAAGGTGAAGGCTC	445
	GAGCCTTCACCTTAGGGTTGCCATAACAGCATCAGGAGAG GACAGATCCCCAAAGGACTCAAAGAACCTCTGGGTCCAAGG GTAGACCACCAGTAATCTGAGGGTAGGAAAACAGCCCAA	446
	GGTTCTTTGAGTCCTTT	447
	AAAGGACTCAAAGAACC	448
Thalassaemia Beta LYS-62-Term AAG to TAG	TTCTTTGAGTCCTTTGGGGATCTGTCCTCTCCTGATGCTGTTA TGGGCAACCCTAAGGTGAAGGCTCATGGCAAGAAGGTGCTA GGTGCCTTTAGTGATGGCCTGGCTCACCTGGACAACC	449
	GGTTGTCCAGGTGAGCCAGGCCATCACTAAAGGCACCTAGC ACCTTCTTGCCATGAGCCTTCACCTTAGGGTTGCCATAACA GCATCAGGAGAGGACAGATCCCCAAAGGACTCAAAGAA	450
	CTAAGGTGAAGGCTCAT	451
	ATGAGCCTTCACCTTAG	452
Thalassaemia Beta SER-73-ARG AGT to AGA	TGCTGTTATGGGCAACCCTAAGGTGAAGGCTCATGGCAAGA AGGTGCTAGGTGCCTTTAGTGATGGCCTGGCTCACCTGGAC AACCTCAAGGGCACTTTTTCTCAGCTGAGTGAGCTGCAC	453
	GTGCAGCTCACTCAGCTGAGAAAAAGTGCCCTTGAGGTTGTC CAGGTGAGCCAGGCCATCACTAAAGGCACCTAGCACCTTCT TGCCATGAGCCTTCACCTTAGGGTTGCCATAACAGCA	454

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCCTTTAGTIGATGGCCT	455
	AGGCCATCACTAAAGGC	456
Haemolytic Anaemia GLY-75-VAL GGC to GTC	TTATGGGCAACCCTAAGGTGAAGGCTCATGGCAAGAAGGTG CTAGGTGCCTTTAGTGATGGCCTGGCTCACCTGGACAACCT CAAGGGCACTTTTTCTCAGCTGAGTGAGCTGCACTGTGA	457
	TCACAGTGCAGCTCACTCAGCTGAGAAAAAGTGCCCTTGAG GTTGTCCAGGTGAGCCAGGCCATCACTAAAGGCACCTAGCA CCTTCTTGCCATGAGCCTTACCTTAGGGTTGCCCATAA	458
	TAGTGATGGCCTGGCTC	459
	GAGCCAGGCCATCACTA	460
Thalassaemia Beta GLU-91-Term GAG to TAG	GCCTTTAGTGATGGCCTGGCTCACCTGGACAACCTCAAGGG CACCTTTGCCACACTGAGTGAGCTGCACTGTGACAAGCTGC ACGTGGATCCTGAGAACTTCAGGGTGAGTCTATGGGACC	461
	GGTCCCATAGACTCACCTGAAGTTCTCAGGATCCACGTGCA GCTTGTACAGTGCAGCTCACTCAGTGTGGCAAAGGTGCCC TTGAGGTTGTCCAGGTGAGCCAGGCCATCACTAAAGGC	462
	CACTGAGTGAGCTGCAC	463
	GTGCAGCTCACTCAGTG	464
Thalassaemia Beta VAL-99-MET GTG to ATG	CTGGACAACCTCAAGGGCACTTTTTCTCAGCTGAGTGAGCTG CACTGTGACAAGCTGCACGTGGATCCTGAGAACTTCAGGGT GAGTCCAGGAGATGCTTCACTTTTCTCTTTTACTTTT	465
	GAAAGTAAAAAGAGAAAAGTGAAGCATCTCCTGGACTCACCC TGAAGTTCTCAGGATCCACGTGCAGCTTGTACAGTGCAGCT CACTCAGCTGAGAAAAAGTGCCCTTGAGGTTGTCCAG	466
	AGCTGCACGTGGATCCT	467
	AGGATCCACGTGCAGCT	468
Thalassaemia Beta LEU-111-PRO CTG-CCG	CCCTTTTGCTAATCATGTTATACCTCTTATCTTCTCCACCA GCTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCACT TTGGCAAAGAATTCACCCACCAAGTGCAGGCTGCCTA	469
	TAGGCAGCCTGCACTGGTGGGGTGAATCTTTGCCAAAGTG ATGGGCCAGCACACAGACCAAGCACGTTGCCAGGAGCTGTG GGAGGAAGATAAGAGGTATGAACATGATTAGCAAAGGG	470
	CAACGTGCTGGTCTGTG	471
	CACAGACCAAGCACGTTG	472

5

10

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Thalassaemia Beta CYS-113-Term TGT to TGA	GCTAATCATGTTACATCCTCTTATCTTCCTCCACAGCTCCTG GGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAA AGAATTCACCCCACCAGTGCAGGCTGCCTATCAGAAA	473
	TTTCTGATAGGCAGCCTGCACTGGTGGGGTGAATTCTTTGCC AAAGTGATGGGCCAGCACACAGACCAGCACGTTGCCAGGA GCTGTGGGAGGAAGATAAGAGGTATGAACATGATTAGC	474
	CTGGTCTGTGTGCTGGC	475
	GCCAGCACACAGACCAG	476
Thalassaemia Beta LEU-115-PRO CTG to CCG	TCATGTTACATCCTCTTATCTTCCTCCACAGCTCCTGGGCA ACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAAGAAT TCACCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGT	477
	ACCACTTTCTGATAGGCAGCCTGCACTGGTGGGGTGAATTCT TTGCCAAAGTGATGGGCCAGCACACAGACCAGCACGTTGCC CAGGAGCTGTGGGAGGAAGATAAGAGGTATGAACATGA	478
	CTGTGTGCTGGCCCATC	479
	GATGGGCCAGCACACAG	480
Thalassaemia Beta ALA-116-ASP GCC to GAC	TGTTACATCCTCTTATCTTCCTCCACAGCTCCTGGGCAACG TGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAAGAATTCA CCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGTGGC	481
	GCCACCACTTTCTGATAGGCAGCCTGCACTGGTGGGGTGAA TTCTTTGCCAAAGTGATGGGCCAGCACACAGACCAGCACGTT GCCCAGGAGCTGTGGGAGGAAGATAAGAGGTATGAACA	482
	TGTGCTGGCCCATCACT	483
	AGTGATGGGCCAGCACACA	484
Thalassaemia Beta GLU-122-Term GAA to TAA	TTCCTCCACAGCTCCTGGGCAACGTGCTGGTCTGTGTGCT GGCCCATCACTTTGGCAAAGAAATTCACCCCACCAGTGCAGG CTGCCTATCAGAAAGTGGTGGCTGGTGTGGCTAATGCC	485
	GGGCATTAGCCACACCAGCCACCACTTTCTGATAGGCAGCC TGCACTGGTGGGGTGAATTCTTTGCCAAAGTGATGGGCCAG CACACAGACCAGCACGTTGCCCAGGAGCTGTGGGAGGAA	486
	TTGGCAAAGAAATTCACC	487
	GGTGAATTCTTTGCCAA	488
Thalassaemia Beta GLN-128-PRO CAG to CCG	GCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAA GAATTCACCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGT GGCTGGTGTGGCTAATGCCCTGGCCACAAGTATCACTA	489

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAGTGATACTTGTGGGCCAGGGCATTAGCCACACCAGCCAC CACTTTCTGATAGGCAGCCTGCACTGGTGGGGTGAATTCTTT GCCAAAGTGATGGGCCAGCACACAGACCAGCACGTTGC	490
	ACCAGTGCAGGCTGCCT	491
	AGGCAGCCTGCACTGGT	492
Thalassaemia Beta GLN-128-Term CAG to TAG	GGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAA AGAATTCACCCCAACAGTGCAAGGCTGCCTATCAGAAAGTGGT GGCTGGTGTGGCTAATGCCCTGGCCACAAGTATCACT	493
	AGTGATACTTGTGGGCCAGGGCATTAGCCACACCAGCCACC ACTTTCTGATAGGCAGCCTGCACTGGTGGGGTGAATTCTTTG CCAAAGTGATGGGCCAGCACACAGACCAGCACGTTGCC	494
	CACCAGTGCAGGCTGCC	495
	GGCAGCCTGCACTGGTG	496
Thalassaemia Beta GLN-132-LYS CAG to AAG	GTCTGTGTGCTGGCCCATCACTTTGGCAAAGAATTCACCCCA CCAGTGCAGGCTGCCTATCAGAAAGTGGTGGCTGGTGTGGC TAATGCCCTGGCCACAAGTATCACTAAGCTCGCTTTC	497
	GAAAGCGAGCTTAGTGATACTTGTGGGCCAGGGCATTAGCC ACACCAGCCACCACTTTCTGATAGGCAGCCTGCACTGGTGG GGTGAATTCTTTGCCAAAGTGATGGGCCAGCACACAGAC	498
	CTGCCTATCAGAAAGTG	499
	CACTTTCTGATAGGCAG	500

EXAMPLE 7 Retinoblastoma

Retinoblastoma (RB) is an embryonic neoplasm of retinal origin. It almost always presents in early childhood and is often bilateral. The risk of osteogenic sarcoma is increased 500-fold in bilateral retinoblastoma patients, the bone malignancy being at sites removed from those exposed to radiation treatment of the eye tumor.

The retinoblastoma susceptibility gene (pRB; pRb) plays a pivotal role in the regulation of the cell cycle. pRB restrains cell cycle progression by maintaining a checkpoint in late G₁ that controls commitment of cells to enter S phase. The critical role that pRB plays in cell cycle regulation explains its

status as archetypal tumor suppressor: loss of pRB function results in an inability to maintain control of the G₁ checkpoint; unchecked progression through the cell cycle is, in turn, a hallmark of neoplasia.

Blanquet *et al.*, *Hum. Molec. Genet.* 4: 383-388 (1995) performed a mutation survey of the RB1 gene in 232 patients with hereditary or nonhereditary retinoblastoma. They systematically explored all 27 exons and flanking sequences, as well as the promoter. All types of point mutations were represented and found to be unequally distributed along the RB1 gene sequence. In the population studied, exons 3, 8, 18, and 19 were preferentially altered. The attached table discloses the correcting oligonucleotide base sequences for the retinoblastoma oligonucleotides of the invention.

Table 13
pRB Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Trp99Term TGG-TAG	AATATTTGATCTTTATTTTTTTGTTCCCAGGGAGGTTATATTCAA AAGAAAAAGGAAGTGTGGGAATCTGTATCTTTATTGCAGCA GTTGACCTAGATGAGATGTCGTTCACTTTTACTGA	501
	TCAGTAAAAGTGAACGACATCTCATCTAGGTCAACTGCTGCA ATAAAGATACAGATTCCCACAGTTTCCTTTTTCTTTGAATATA ACCTCCCTGGGAACAAAAATAAAGATCAAATATT	502
	GGAAGTGTGGGAATCT	503
	AGATTCCTCCACAGTTCC	504
Retinoblastoma Glu137Asp GAA-GAT	ATTTACTTTTTTCTATTCTTTCTTTGTAGTGTCCATAAATTCTT TAACTTACTAAAAGAAATTGATACCAGTACCAAAGTTGATAAT GCTATGTCAAGACTGTTGAAGAAGTATGATGTA	505
	TACATCATACTTCTTCAACAGTCTTGACATAGCATTATCAACTT TGGTACTGGTATCAATTCTTTTAGTAAGTTAAAGAATTTATGG ACACTACAAAGGAAAGAATAGAAAAAAGTAAAT	506
	CTAAAAGAAATTGATAC	507
	GTATCAATTCTTTTAG	508
Retinoblastoma Glu137Term GAA-TAA	TGATTTACTTTTTTCTATTCTTTCTTTGTAGTGTCCATAAATT CTTTAACTTACTAAAAGAAATTGATACCAGTACCAAAGTTGAT AATGCTATGTCAAGACTGTTGAAGAAGTATGATG	509

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CATCATACTTCTTCAACAGTCTTGACATAGCATTATCAACTTT GGTACTGGTATCAATTTCTTTTAGTAAGTTAAAGAATTTATGG ACACTACAAAGGAAAGAATAGAAAAAAGTAAATCA	510
	TACTAAAAGAAATTGAT	511
	ATCAATTTCTTTTAGTA	512
Retinoblastoma Gln176Term CAA-TAA	AAAATGTTAAAAAGTCATAATGTTTTCTTTTCAGGACATGTGA ACTTATATATTTGACACAACCCAGCAGTTCGTAAGTAGTTCAC AGAATGTTATTTTCACTTAAAAAAGATTTT	513
	AAAATCTTTTTTTTTAAGTGAAAAATAACATTCTGTGAAGTACT TACGAAGTCTGGGTTGTGTCAAATATATAAGTTCACATGTCC TGAAAAGAAAAACATTATGACTTTTTAACATTTT	514
	ATTGACACAACCCAGC	515
	GCTGGGTTGTGTCAAAT	516
Retinoblastoma Ile185Thr ATA-ACA	TGATACATTTTTCTGTTTTTTTTCTGCTTTCTATTTGTTAATA GGATATCTACTGAAATAAATTCTGCATTGGTGCTAAAAGTTTC TTGGATCACATTTTTATTAGCTAAAGGTAAGTT	517
	AACCTACCTTTAGCTAATAAAAAATGTGATCCAAGAACTTTTA GCACCAATGCAGAATTTATTTTCAGTAGATATCCTATTAAACAA ATAGAAAGCAGAAAAAACAGGAAAAATGTATCA	518
	TACTGAAATAAATTCTG	519
	CAGAATTTATTTTCAGTA	520
Retinoblastoma Gln207Term CAA-TAA	AAAGATCTGAATCTCTAACTTTCTTTAAAAATGTACATTTTTTT TTCAGGGGAAGTATTACAAATGGAAGATGATCTGGTGATTTTC ATTTTCAGTTAATGCTATGTGTCCTTGACTATTTTA	521
	TAAAATAGTCAAGGACACATAGCATTAACTGAAATGAAATCAC CAGATCATCTTCATTTGTAATACTTCCCCTGAAAAAATG TACATTTTTAAAGAAAGTTAGAGATTCAGATCTTT	522
	AAGTATTACAATGGAA	523
	TTCCATTTGTAATACTT	524
Retinoblastoma Arg251Term CGA to TGA	GTTCTTATCTAATTTACCACTTTTACAGAAACAGCTGTTATACC CATTAAATGGTTCACCTCGAACACCCAGGCGAGGTGAGAACA GGAGTGCACGGATAGCAAAACAAGTAAAGTATA	525
	TATCATTTTCTAGTTGTTTTGCTATCCGTCGACTCCTGTTCTG ACCTCGCCTGGGTGTTCCGAGGTGAACCATTAAATGGGTATAAC AGCTGTTTCTGTAAAGTGGTAAATTAGATAAGAAC	526

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GTTACACCT <u>C</u> GAACACCC	527
	GGGTGTT <u>C</u> GAGGTGAAC	528
Retinoblastoma Arg255Term CGA to TGA	TTTACCACTTTTACAGAAACAGCTGTTATACCCATTAAATGGTT CACCTCGAACACCCAGG <u>C</u> GAGGTCAGAACAGGAGTGCACG GATAGCAAAACAAGTAGAAAATGATACAAGAATTATTG	529
	CAATAATTCTTGTATCATTTTCTAGTTGTTTTGCTATCCGTGCA CTCCTGTTCTGACCT <u>C</u> GCTGGGTGTTGAGGTGAACCATT ATGGGTATAACAGCTGTTTCTGTAAAAGTGGTAAA	530
	CACCCAGG <u>C</u> GAGGTCAG	531
	CTGACCT <u>C</u> GCTGGGTG	532
Retinoblastoma Gln266Term CAA to TAA	ATTAATGGTTCACCTCGAACACCCAGGCGAGGTCAGAACAG GAGTGCACGGATAGCAAAACAAGTAGAAAATGATACAAGAAT TATTGAAGTTCTCTGTAAAGAACATGAATGTAATATAG	533
	CTATATTACATTCATGTTCTTTACAGAGAACTTCAATAATTCTT GTATCATTTTCTAGTT <u>G</u> TTTTGCTATCCGTGCACTCCTGTTCT GACCTCGCCTGGGTGTTGAGGTGAACCATTAAAT	534
	TAGCAAAACAAGTAGAA	535
	TTCTAGTT <u>G</u> TTTTGCTA	536
Retinoblastoma Arg320Term CGA to TGA	TGACATGTAAAGGATAATTGTCAGTGACTTTTTCTTTCAAGG TTGAAAATCTTTCTAAACGATACGAAGAAATTTATCTTAAAAAT AAAGATCTAGATGCAAGATTATTTTTGGATCATG	537
	CATGATCCAAAAATAATCTTGCATCTAGATCTTTATTTTAAAGA TAAATTTCTTCGTATC <u>G</u> TTTAGAAAGATTTTCAACCTTGAAAGA AAAAAGTCACTGACAATTATCCTTTACATGTCA	538
	TTTCTAAACGATACGAA	539
	TTCGTATC <u>G</u> TTTAGAAA	540
Retinoblastoma Gln354Term CAG to TAG	ACAAATTGTAAATTTTTCAGTATGTGAATGACTTCACTTATTGTT ATTTAGTTTTGAAACA <u>C</u> AGAGAACACCACGAAAAAGTAACCTT GATGAAGAGGTGAATGTAATTCCTCCACACACTC	541
	GAGTGTGTGGAGGAATTACATTCACCTCTTCATCAAGGTTAC TTTTTCGTGGTGTCTCT <u>G</u> TGTTTCAAACTAAATAACAATAA GTGAAGTCATTCACATACTGAAAATTTACAATTTGT	542
	TTGAAACA <u>C</u> AGAGAACA	543
	TGTTCTCT <u>G</u> TGTTTCAA	544

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Arg358Gly CGA to GGA	TTTTCAGTATGTGAATGACTTCACTTATTGTTATTTAGTTTTGA AACACAGAGAACACCACGAAAAAGTAACCTTGATGAAGAGGT GAATGTAATTCCTCCACACACTCCAGTTAGGTATG	545
	CATACCTAACTGGAGTGTGTGGAGGAATTACATTCACCTCTT CATCAAGGTTACTTTTTCTGGTGTCTCTGTGTTTCAAACT AAATAACAATAAGTGAAGTCATTCACATACTGAAAA	546
	GAACACCACGAAAAAGT	547
	ACTTTTTCTGGTGTTC	548
Retinoblastoma Arg358Term CGA to TGA	TTTTCAGTATGTGAATGACTTCACTTATTGTTATTTAGTTTTGA AACACAGAGAACACCACGAAAAAGTAACCTTGATGAAGAGGT GAATGTAATTCCTCCACACACTCCAGTTAGGTATG	549
	CATACCTAACTGGAGTGTGTGGAGGAATTACATTCACCTCTT CATCAAGGTTACTTTTTCTGGTGTCTCTGTGTTTCAAACT AAATAACAATAAGTGAAGTCATTCACATACTGAAAA	550
	GAACACCACGAAAAAGT	551
	ACTTTTTCTGGTGTTC	552
Retinoblastoma Ser397Term TCA to TAA	CTGTTATGAACACTATCCAACAATTAATGATGATTTTAAATTCA GCAAGTGATCAACCTTCAGAAAATCTGATTTCTATTTTAAACG TAAGCCATATATGAAACATTATTTATTGTAATAT	553
	ATATTACAATAAATAATGTTTCATATATGGCTTACGTTAAAATA GGAAATCAGATTTTCTGAAGGTTGATCACTTGCTGAATTTAA ATCATCATTAAATTGTTGGATAGTGTTCAACAG	554
	TCAACCTTCAGAAAATC	555
	GATTTTCTGAAGGTTGA	556
Retinoblastoma Arg445Term CGA to TGA	TTTCATAATTGTGATTTTCTAAAATAGCAGGCTCTTATTTTCT TTTTGTTTGTGTAGCGATACAACTTGGAGTTGCTTGTAT TACCGAGTAATGGAATCCATGCTTAAATCAGTAA	557
	TACTGATTTAAGCATGGATTCCATTACTCGGTAATACAAGCG AACTCCAAGTTTGTATCGCTACAAACAAACAAAAAGAAAAATA AGAGCCTGCTATTTTAGAAAATCACATTATGAAA	558
	GTTTGTAGCGATACAAA	559
	TTTGTATCGCTACAAAC	560
Retinoblastoma Arg455Term CGA to TGA	GCTCTTATTTTCTTTTGTGTTTGTAGCGATACAACTTGG AGTTGCTTGTATTACCGAGTAATGGAATCCATGCTTAAATCA GTAAGTTAAAAACAATATAAAAAATTTAGCCG	561

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGGCTGAAATTTTTTATATTGTTTTAACTTACTGATTTAAGC ATGGATTCCATTACTCGGTAATACAAGCGAACTCCAAGTTTGT ATCGCTACAAACAAACAAAAAGAAAAATAAGAGC	562
	TGTATTACCGAGTAATG	563
	CATTACTCGGTAATACA	564
Retinoblastoma Arg552Term CGA to TGA	ATCGAAAGTTTTATCAAAGCAGAAGGCAACTTGACAAGAGAA ATGATAAAACATTTAGAACGATGTGAACATCGAATCATGGAAT CCCTTGCATGGCTCTCAGTAAGTAGCTAAATAATTG	565
	CAATTATTTAGCTACTTACTGAGAGCCATGCAAGGGATTCCAT GATTCGATGTTTACATCGTTCTAAATGTTTTATCATTCTCTTG TCAAGTTGCCCTTCTGCTTTGATAAACTTTTCGAT	566
	ATTTAGAACGATGTGAA	567
	TTCACATCGTTCTAAAT	568
Retinoblastoma Cys553Term TGT to TGA	AAGTTTTATCAAAGCAGAAGGCAACTTGACAAGAGAAATGATA AAACATTTAGAACGATGTGAACATCGAATCATGGAATCCCTTG CATGGCTCTCAGTAAGTAGCTAAATAATTGAAGAA	569
	TTCTTCAATTATTTAGCTACTTACTGAGAGCCATGCAAGGGAT TCCATGATTGATGTTTACATCGTTCTAAATGTTTTATCATTTC TCTTGTCAAGTTGCCCTTCTGCTTTGATAAACTT	570
	GAACGATGTGAACATCG	571
	CGATGTTTACATCGTTC	572
Retinoblastoma Glu554Term GAA to TAA	AGTTTTATCAAAGCAGAAGGCAACTTGACAAGAGAAATGATA AACATTTAGAACGATGTGAACATCGAATCATGGAATCCCTTG CATGGCTCTCAGTAAGTAGCTAAATAATTGAAGAAA	573
	TTTCTTCAATTATTTAGCTACTTACTGAGAGCCATGCAAGGGA TTCCATGATTGATGTTTACATCGTTCTAAATGTTTTATCATTT CTCTTGTCAAGTTGCCTTCTGCTTTGATAAACT	574
	AACGATGTGAACATCGA	575
	TCGATGTTTACATCGTT	576
Retinoblastoma Ser567Leu TCA to TTA	TACCTGGGAAAATTATGCTTACTAATGTGGTTTTAATTTATC ATGTTTCATATAGGATTACCTTTATTTGATCTTATTAACAAT CAAAGGACCGAGAAGGACCAACTGATCACCTTGA	577
	TCAAGGTGATCAGTTGGTCCTTCTCGGTCCTTTGATTGTTTAA TAAGATCAAATAAAGGTGAATCCTATATGAAACATGATGAAAT TAAACCACATTAGTAAGCATAATTTCCAGGTA	578

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATAGGATT <u>C</u> ACCTTTAT	579
	ATAAAGGT <u>G</u> AATCCTAT	580
Retinoblastoma Gln575Term CAA to TAA	AATGTGGTTTTAATTTTCATCATGTTTCATATAGGATTACACCTTT ATTTGATCTTATTAA <u>C</u> AATCAAAGGACCGAGAAGGACCAACT GATCACCTTGAATCTGCTTGTCTCTTAATCTTC	581
	GAAGATTAAGAGGACAAGCAGATTCAAGGTGATCAGTTGGTC CTTCTCGGTCCTTTGATT <u>G</u> TTTAATAAGATCAAATAAAGGTGA ATCCTATATGAAACATGATGAAATTAACCACATT	582
	TTATTAA <u>C</u> AATCAAAG	583
	CTTTGATT <u>G</u> TTTAATAA	584
Retinoblastoma Arg579Term CGA to TGA	ATTTTCATCATGTTTCATATAGGATTACACCTTTATTTGATCTTAT TAAACAATCAAAGGAC <u>C</u> GAGAAGGACCAACTGATCACCTTGA ATCTGCTTGTCTCTTAATCTTCCTCTCCAGAATA	585
	TATTCTGGAGAGGAAGATTAAGAGGACAAGCAGATTCAAGGT GATCAGTTGGTCCTTCTC <u>G</u> GTCCTTTGATTGTTTAATAAGATC AAATAAAGGTGAATCCTATATGAAACATGATGAAAT	586
	CAAAGGAC <u>C</u> GAGAAGGA	587
	TCCTTCTC <u>G</u> GTCCTTTG	588
Retinoblastoma Glu580Term GAA to TAA	TCATCATGTTTCATATAGGATTACACCTTTATTTGATCTTATTAA ACAATCAAAGGACCGA <u>G</u> AAGGACCAACTGATCACCTTGAATC TGCTTGTCTCTTAATCTTCCTCTCCAGAATAATC	589
	GATTATTCTGGAGAGGAAGATTAAGAGGACAAGCAGATTCAA GGTGATCAGTTGGTCCTT <u>C</u> TCGGTCCTTTGATTGTTTAATAAG ATCAAATAAAGGTGAATCCTATATGAAACATGATGA	590
	AGGACCGA <u>G</u> AAGGACCA	591
	TGGTCCTT <u>C</u> TCGGTCCT	592
Retinoblastoma Ser634Term TCA to TGA	AGAAAAAGGTTCAACTACGCGTGTAATTCTACTGCAAATG CAGAGACACAAGCAACCT <u>C</u> AGCCTTCCAGACCCAGAAGCCA TTGAAATCTACCTCTCTTTCACTGTTTTATAAAAAAGG	593
	CCTTTTTTATAAAACAGTGAAAGAGAGGTAGATTTCAATGGCT TCTGGGTCTGGAAGGCT <u>G</u> AGGTTGCTTGTGTCTCTGCATTG CAGTAGAATTTACACGCGTAGTTGAACCTTTTTCT	594
	AGCAACCT <u>C</u> AGCCTTCC	595
	GGAAGGCT <u>G</u> AGGTTGCT	596

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Ala635Pro GCC to CCC	AAAAAAGGTTCAACTACGCGTGTAATTCTACTGCAAATGCA GAGACACAAGCAACCTCAGCCTTCCAGACCCAGAAGCCATT GAAATCTACCTCTCTTTCACTGTTTTATAAAAAAGGTT	597
	AACCTTTTTTATAAAACAGTGAAAGAGAGGTAGATTTCAATGG CTTCTGGGTCTGGAAGGCTGAGGTTGCTTGTGTCTCTGCATT TGCAGTAGAATTTACACGCGTAGTTGAACCTTTTTT	598
	CAACCTCAGCCTTCCAG	599
	CTGGAAGGCTGAGGTTG	600
Retinoblastoma Gln639Term CAG to TAG	ACTACGCGTGTAATTCTACTGCAAATGCAGAGACACAAGCA ACCTCAGCCTTCCAGACCCAGAAGCCATTGAAATCTACCTCT CTTCACTGTTTTATAAAAAAGGTTAGTAGATGATTA	601
	TAATCATCTACTAACCTTTTTTATAAAACAGTGAAAGAGAGGT AGATTTCAATGGCTTCTGGGTCTGGAAGGCTGAGGTTGCTTG TGTCTCTGCATTTGCAGTAGAATTTACACGCGTAGT	602
	TCCAGACCCAGAAGCCA	603
	TGGCTTCTGGGTCTGGA	604
Retinoblastoma Leu657Pro CTA to CCA	TTGTAATTCAAAATGAACAGTAAAAATGACTAATTTTTCTTATT CCCACAGTGTATCGGCTAGCCTATCTCCGGCTAAATACACTT TGTGAACGCCTTCTGTCTGAGCACCCAGAATTAGA	605
	TCTAATTCTGGGTGCTCAGACAGAAGGCGTTCACAAAGTGTA TTTAGCCGGAGATAGGCTAGCCGATACTGTGGGAATAAG AAAAATTAGTCATTTTTACTGTTTCATTTTGAATTACAA	606
	GTATCGGCTAGCCTATC	607
	GATAGGCTAGCCGATAC	608
Retinoblastoma Arg661Trp CGG to TGG	AATGAACAGTAAAAATGACTAATTTTTCTTATTCCCACAGTGTA TCGGCTAGCCTATCTCCGGCTAAATACACTTTGTGAACGCCT TCTGTCTGAGCACCCAGAATTAGAACATATCATCT	609
	AGATGATATGTTCTAATTCTGGGTGCTCAGACAGAAGGCGTT CACAAAGTGATTTAGCCGGAGATAGGCTAGCCGATACTGT TGGGAATAAGAAAAATTAGTCATTTTTACTGTTTCAAT	610
	CCTATCTCCGGCTAAAT	611
	ATTTAGCCGGAGATAGG	612
Retinoblastoma Leu662Pro CTA to CCA	AACAGTAAAAATGACTAATTTTTCTTATCCCACAGTGTATCG GCTAGCCTATCTCCGGCTAAATACACTTTGTGAACGCCTTCT GTCTGAGCACCCAGAATTAGAACATATCATCTGGAC	613

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GTCCAGATGATATGTTCTAATTCTGGGTGCTCAGACAGAAGG CGTTCACAAAGTGTATTTAGCCGGAGATAGGCTAGCCGATAC ACTGTGGGAATAAGAAAAATTAGTCATTTTTACTGTT	614
	TCTCCGGCTAAATACAC	615
	GTGTATTTAGCCGGAGA	616
Retinoblastoma Glu675Term GAA to TAA	TATCGGCTAGCCTATCTCCGGCTAAATACACTTTGTGAACGC CTTCTGTCTGAGCACCCAGAAATTAGAACATATCATCTGGACC CTTTCCAGCACACCCTGCAGAATGAGTATGAACTCA	617
	TGAGTTCATACTCATTCTGCAGGGTGTGCTGGAAAAGGGTCC AGATGATATGTTCTAATTCTGGGTGCTCAGACAGAAGGCGTT CACAAAGTGTATTTAGCCGGAGATAGGCTAGCCGATA	618
	AGCACCCAGAAATTAGAA	619
	TTCTAATTCTGGGTGCT	620
Retinoblastoma Gln685Pro CAG to CCG	TTTGTGAACGCCTTCTGTCTGAGCACCCAGAATTAGAACATA TCATCTGGACCCTTTTCCAGCACACCCTGCAGAATGAGTATG AACTCATGAGAGACAGGCATTTGGACCAAGTAAGAAA	621
	TTTCTTACTTGGTCCAAATGCCTGTCTCTCATGAGTTCATACT CATTCTGCAGGGTGTGCTGGAAAAGGGTCCAGATGATATGTT CTAATTCTGGGTGCTCAGACAGAAGGCGTTCACAAA	622
	CCTTTTCCAGCACACC	623
	GGGTGTGCTGGAAAAGG	624
Retinoblastoma Cys706Tyr TGT to TAT	AAAACCATGTAATAAAATTCTGACTACTTTTACATCAATTTATT TACTAGATTATGATGTGTTCCATGTATGGCATATGCAAAGTGA AGAATATAGACCTTAAATTCAAAATCATTGTAAC	625
	GTTACAATGATTTTGAATTTAAGGTCTATATTCTTCACTTTGCA TATGCCATACATGGAACACATCATAATCTAGTAAATAAATTGA TGTAAGTAGTCAGAAATTTATTACATGGTTTT	626
	TATGATGTGTTCCATGT	627
	ACATGGAACACATCATA	628
Retinoblastoma Cys712Arg TGC to CGC	TTCTGACTACTTTTACATCAATTTATTTACTAGATTATGATGTG TTCCATGTATGGCATAIGCAAAGTGAAGAATATAGACCTTAAA TTCAAATCATTGTAACAGCATACAAGGATCTTC	629
	GAAGATCCTTGTATGCTGTTACAATGATTTTGAATTTAAGGTC TATATTCTTCACTTTGCATATGCCATACATGGAACACATCATA ATCTAGTAAATAAATTGATGTAAAAGTAGTCAGAA	630

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGGCATATGCAAAGTG	631
	CACTTTGCATATGCCAT	632
Retinoblastoma Tyr728Term TAC to TAA	GTATGGCATATGCAAAGTGAAGAATATAGACCTTAAATTCAAA ATCATTGTAACAGCATACAAGGATCTTCCTCATGCTGTTGAG GAGGTAGGTAATTTTCCATAGTAAGTTTTTTTGATA	633
	TATCAAAAAAAGTACTATGGAAAATTACCTACCTCCTGAACA GCATGAGGAAGATCCTTGATGCTGTTACAATGATTTTGAATT TAAGGTCTATATTCTTCACTTTGCATATGCCATAC	634
	ACAGCATACAAGGATCT	635
	AGATCCTTGATGCTGT	636
Retinoblastoma Glu748Term GAG to TAG	TTTTTTTTTTTTTACTGTTCTTCCTCAGACATTCAAACGTGT TTTGATCAAAGAAGAGGAGTATGATTCTATTATAGTATTCTATA ACTCGGTCTTCATGCAGAGACTGAAAACAAATA	637
	TATTTGTTTTAGTCTCTGCATGAAGACCGAGTTATAGAATAC TATAATAGAATCATACTCCTCTCTTTGATCAAAACACGTTTGA ATGTCTGAGGAAGAACAGTAAAAAAAAAAAAAAAA	638
	AAGAAGAGGAGTATGAT	639
	ATCATACTCCTCTTCTT	640
Retinoblastoma Gln762Term CAG to TAG	GTTTTGATCAAAGAAGAGGAGTATGATTCTATTATAGTATTCT ATAACTCGGTCTTCATGCAGAGACTGAAAACAAATATTTTGCA GTATGCTTCCACCAGGGTAGGTCAAAAGTATCCTT	641
	AAGGATACTTTTGACCTACCCTGGTGAAGCATACTGCAAAA TATTTGTTTTAGTCTCTGCATGAAGACCGAGTTATAGAATAC TATAATAGAATCATACTCCTCTCTTTGATCAAAAC	642
	TCTTCATGCAGAGACTG	643
	CAGTCTCTGCATGAAGA	644
Retinoblastoma Arg787Term CGA-TGA	TAATCTACTTTTTGTTTTGCTCTAGCCCCCTACCTTGTCAC CAATACCTCACATTCTCGAAGCCCTTACAAGTTTCCTAGTTC ACCCTTACGGATTCTGGAGGGGAACATCTATATT	645
	AAATATAGATGTTCCCTCCAGGAATCCGTAAGGGTGAAGTAG GAACTTGTAAGGGCTTCGAGGAATGTGAGGTATTGGTGACA AGGTAGGGGGCTAGAGCAAAAACAAAAAGTAGATTA	646
	ACATTCCTCGAAGCCCT	647
	AGGGCTTCGAGGAATGT	648

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Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Ser816Term TCA to TGA	CCTTACGGATTCTGGAGGGAACATCTATATTTACCCCCTGA AGAGTCCATATAAAATTTGAGAAGGTCTGCCAACACCAACAA AAATGACTCCAAGATCAAGGTGTGTGTTTTCTCTTTA	649
	TAAAGAGAAAACACACACCTTGATCTTGGAGTCATTTTTGTTG GTGTTGGCAGACCTTCTGAAATTTATATGGACTCTTCAGGG GTGAAATATAGATGTTCCCTCCAGGAATCCGTAAGG	650
	TAAATTTGAGAAGGTC	651
	GACCTTCTGAAATTTTA	652

EXAMPLE 8 BRCA1 and BRCA2

Breast cancer is the second major cause of cancer death in American women, with an estimated 44,190 lives lost (290 men and 43,900 women) in the US in 1997. While ovarian cancer accounts for fewer deaths than breast cancer, it still represents 4% of all female cancers. In 1994, two breast cancer susceptibility genes were identified: BRCA1 on chromosome 17 and BRCA2 on chromosome 13. When a woman carries a mutation in either BRCA1 or BRCA2, she is at increased risk of being diagnosed with breast or ovarian cancer at some point in her life.

Ford *et al.*, *Am. J. Hum. Genet.* 62: 676-689 (1998) assessed the contribution of BRCA1 and BRCA2 to inherited breast cancer by linkage and mutation analysis in 237 families, each with at least 4 cases of breast cancer. Families were included without regard to the occurrence of ovarian or other cancers. Overall, disease was linked to BRCA1 in an estimated 52% of families, to BRCA2 in 32% of families, and to neither gene in 16%, suggesting other predisposition genes. The majority (81%) of the breast-ovarian cancer families were due to BRCA1, with most others (14%) due to BRCA2. Conversely, the majority (76%) of families with both male and female breast cancer were due to BRCA2. The largest proportion (67%) of families due to other genes were families with 4 or 5 cases of female breast cancer only.

More than 75% of the reported mutations in the BRCA1 gene result in truncated proteins. Couch *et al.*, *Hum. Mutat.* 8: 8-18, 1996. (1996) reported a total of 254 BRCA1 mutations, 132 (52%) of which were unique. A total of 221 (87%) of all mutations or 107 (81%) of the unique mutations are small deletions, insertions, nonsense point mutations, splice variants, and regulatory mutations that result in

truncation or absence of the BRCA1 protein. A total of 11 disease-associated missense mutations (5 unique) and 21 variants (19 unique) as yet unclassified as missense mutations or polymorphisms had been detected. Thirty-five independent benign polymorphisms had been described. The most common mutations were 185delAG and 5382insC, which accounted for 30 (11.7%) and 26 (10.1%), respectively, of all the mutations.

Most BRCA2 mutations are predicted to result in a truncated protein product. The smallest known cancer-associated deletion removes from the C terminus only 224 of the 3,418 residues constituting BRCA2, suggesting that these terminal amino acids are critical for BRCA2 function. Studies (Spain *et al.*, Proc. Natl. Acad. Sci. 96:13920-13925 (1999)) suggest that such truncations eliminate or interfere with 2 nuclear localization signals that reside within the final 156 residues of BRCA2, suggesting that the vast majority of BRCA2 mutants are nonfunctional because they are not translocated into the nucleus.

The attached table discloses the correcting oligonucleotide base sequences for the BRCA1 and BRCA2 oligonucleotides of the invention.

Table 14
BRCA1 Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Met-1-Ile ATG to ATT	CTGCGCTCAGGAGGCCTTCACCCTCTGCTCTGGGTAAAGTT CATTGGAACAGAAAGAAATGGATTTATCTGCTCTTCGCGTTG AAGAAGTACAAAATGTCATTAATGCTATGCAGAAAATC	653
	GATTTTCTGCATAGCATTAAATGACATTTTGTACTTCTTCAACG CGAAGAGCAGATAAATCCATTTCTTTCTGTTCCAATGAACCTT ACCCAGAGCAGAGGGTGAAGGCCTCCTGAGCGCAG	654
	AAAGAAATGGATTTATC	655
	GATAAATCCATTTCTTT	656
Breast Cancer Val-11-Ala GTA to GCA	CTGGGTAAAGTTCATTGGAACAGAAAGAAATGGATTTATCTG CTCTTCGCGTTGAAGAAGTACAAAATGTCATTAATGCTATGCA GAAAATCTTAGAGTGTCCCATCTGTCTGGAGTTGAT	657
	ATCAACTCCAGACAGATGGGACACTCTAAGATTTTCTGCATA GCATTAATGACATTTTGTACTTCTTCAACGCGAAGAGCAGATA AATCCATTTCTTCTGTTCCAATGAACCTTACCCAG	658
	TGAAGAAGTACAAAATG	659

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CATTTTGT <u>A</u> CTTCTTCA	660
Breast Cancer Ile-21-Val ATC to GTC	ATGGATTTATCTGCTCTTCGCGTTGAAGAAGTACAAAATGTCA TTAATGCTATGCAGAAA <u>A</u> TCTTAGAGTGTCCCATCTGTCTGG AGTTGATCAAGGAACCTGTCTCCACAAAGTGTGACC	661
	GGTCACACTTTGTGGAGACAGGTTCCCTTGATCAACTCCAGAC AGATGGGACACTCTAAGA <u>T</u> TTTCTGCATAGCATTAAATGACATT TTGTA <u>T</u> CTTCTTCAACGCGAAGAGCAGATAAATCCAT	662
	TGCAGAAA <u>A</u> TCTTAGAG	663
	CTCTAAGATTTTCTGCA	664
Breast Cancer Leu-22-Ser TTA to TCA	ATTTATCTGCTCTTCGCGTTGAAGAAGTACAAAATGTCATTAA TGCTATGCAGAAAATCTT <u>A</u> GAGTGTCCCATCTGTCTGGAGTT GATCAAGGAACCTGTCTCCACAAAGTGTGACCACAT	665
	ATGTGGTCACACTTTGTGGAGACAGGTTCCCTTGATCAACTCC AGACAGATGGGACACTCT <u>A</u> AGATTTTCTGCATAGCATTAAATG ACATTTTGTACTTCTTCAACGCGAAGAGCAGATAAAT	666
	GAAAATCTT <u>A</u> GAGTGTC	667
	GACACTCT <u>A</u> AGATTTTC	668
Breast Cancer Cys-39-Tyr TGT to TAT	AGAAAATCTTAGAGTGTCCCATCTGTCTGGAGTTGATCAAGG AACCTGTCTCCACAAAGT <u>G</u> TGACCACATATTTTGCAAATTTTG CATGCTGAACTTCTCAACCAGAAGAAAGGGCCTTC	669
	GAAGGCCCTTTCTTCTGGTTGAGAAGTTTCAGCATGCAAAT TTGCAAATATGTGGTCA <u>C</u> ACTTTGTGGAGACAGGTTCCCTTG ATCAACTCCAGACAGATGGGACACTCTAAGATTTTCT	670
	CACAAAGT <u>G</u> TGACCACA	671
	TGTGGTCA <u>C</u> ACTTTGTG	672
Breast Cancer Cys-61-Gly TGT to GGT	CACATATTTTGCAAATTTTGCATGCTGAAACTTCTCAACCAGA AGAAAGGGCCTTCACAGTGTCTTTATGTAAGAATGATATAAC CAAAGGAGCCTACAAGAAAGTACGAGATTTAGTC	673
	GACTAAATCTCGTACTTTCTTGTAGGCTCCTTTTGGTTATATC ATTCTTACATAAAGGAC <u>A</u> CTGTGAAGGCCCTTTCTTCTGGTT GAGAAGTTTCAGCATGCAAATTTGCAAATATGTG	674
	CTTCACAGT <u>G</u> TCCTTTA	675
	TAAAGGAC <u>A</u> CTGTGAAG	676

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Leu-63-Stop TTA to TAA	TTTGCAAATTTTGCATGCTGAACTTCTCAACCAGAAGAAAGG GCCTTCACAGTGTCTTTATGTAAGAATGATATAACCAAAGG AGCCTACAAGAAAGTACGAGATTTAGTCAACTTGT	677
	ACAAGTTGACTAAATCTCGTACTTTCTTGTAGGCTCCTTTTGG TTATATCATTCTTACATAAAGGACACTGTGAAGGCCCTTTCTT CTGGTTGAGAAGTTTCAGCATGCAAAATTTGCAA	678
	GTGTCCTTTATGTAAGA	679
	TCTTACATAAAGGACAC	680
Breast Cancer Cys-64-Arg TGT to CGT	TGCAAATTTTGCATGCTGAACTTCTCAACCAGAAGAAAGGG CCTTCACAGTGTCTTTATGTAAGAATGATATAACCAAAGGA GCCTACAAGAAAGTACGAGATTTAGTCAACTTGTTG	681
Breast Cancer Cys-64-Gly TGT to GGT	CAACAAGTTGACTAAATCTCGTACTTTCTTGTAGGCTCCTTTT GGTTATATCATTCTTACATAAAGGACACTGTGAAGGCCCTTTC TTCTGGTTGAGAAGTTTCAGCATGCAAAATTTGCA	682
	GTCCTTTATGTAAGAAT	683
	ATTCTTACATAAAGGAC	684
Breast Cancer Cys-64-Tyr TGT to TAT	GCAAATTTTGCATGCTGAACTTCTCAACCAGAAGAAAGGGC CTTCACAGTGTCTTTATGTAAGAATGATATAACCAAAGGAG CCTACAAGAAAGTACGAGATTTAGTCAACTTGTTGA	685
	TCAACAAGTTGACTAAATCTCGTACTTTCTTGTAGGCTCCTTT TGGTTATATCATTCTTACATAAAGGACACTGTGAAGGCCCTTT CTTCTGGTTGAGAAGTTTCAGCATGCAAAATTTGC	686
	TCCTTTATGTAAGAATG	687
	CATTCTTACATAAAGGA	688
Breast Cancer Gln-74-Stop CAA to TAA	CAGAAGAAAGGGCCTTCACAGTGTCTTTATGTAAGAATGAT ATAACCAAAGGAGCCTACAAGAAAGTACGAGATTTAGTCAA CTTGTTGAAGAGCTATTGAAAATCATTGTGCTTTTC	689
	GAAAAGCACAAATGATTTTCAATAGCTCTTCAACAAGTTGACT AAATCTCGTACTTTCTTGTAGGCTCCTTTTGGTTATATCATTCT TACATAAAGGACACTGTGAAGGCCCTTTCTTCTG	690
	GGAGCCTACAAGAAAGT	691
	ACTTTCTTGTAGGCTCC	692

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Tyr-105-Cys TAT to TGT	AGCTATTGAAAATCATTTGTGCTTTTCAGCTTGACACAGGTTT GGAGTATGCAAACAGCTATAATTTTGCAAAAAAGGAAAATAAC TCTCCTGAACATCTAAAAGATGAAGTTTCTATCAT	693
	ATGATAGAACTTCATCTTTTAGATGTTGAGGAGAGTTATTTT CCTTTTTTGC AAAATTATAGCTGTTTGCATACTCCAAACCTGT GTCAAGCTGAAAAGCACAAATGATTTTCAATAGCT	694
	AAACAGCTATAATTTTG	695
	CAAAATTATAGCTGTTT	696
Breast Cancer Asn-158-Tyr AAC to TAC	CTACAGAGTGAACCCGAAAATCCTTCCTTGCAGGAAACCAGT CTCAGTGTCCAACCTCTCTAACCTTGGAAGTGTGAGAACTCTG AGGACAAAGCAGCGGATACAACCTCAAAGACGTCTG	697
	CAGACGTCTTTTGAGGTTGTATCCGCTGCTTTGTCCTCAGAG TTCTCACAGTTCCAAGGTAGAGAGTTGGACACTGAGACTGG TTTCTGCAAGGAAGGATTTTCGGGTTCACTCTGTAG	698
	AACCTCTCTAACCTTGGA	699
	TCCAAGGTTAGAGAGTT	700
Breast Cancer Gln-169-Stop CAG to TAG	GAAACCAGTCTCAGTGTCCAACCTCTTAACCTTGGAAGTGTG AGAACTCTGAGGACAAAGCAGCGGATACAACCTCAAAGAC GTCTGTCTACATTGAATTGGGATCTGATTCTTCTGAAG	701
	CTTCAGAAGAATCAGATCCCAATTCAATGTAGACAGACGTCTT TTGAGGTTGTATCCGCTGCTTTGTCCTCAGAGTTCTCACAGT TCCAAGGTTAGAGAGTTGGACACTGAGACTGGTTTC	702
	GGACAAAGCAGCGGATA	703
	TATCCGCTGCTTTGTCC	704
Breast Cancer Trp-353-Stop TGG to TAG	CTCCCAGCACAGAAAAAAGGTAGATCTGAATGCTGATCCCC TGTGTGAGAGAAAAGAATGGAATAAGCAGAACTGCCATGCT CAGAGAATCCTAGAGATACTGAAGATGTTCTTGGAT	705
	ATCCAAGGAACATCTTCAGTATCTCTAGGATTCTCTGAGCAT GGCAGTTTCTGCTTATTCCATTCTTTTCTCTCACACAGGGGAT CAGCATTGAGATCTACCTTTTTTCTGTGCTGGGAG	706
	AAAAGAATGGAATAAGC	707
	GCTTATTCCATTCTTTT	708
Breast Cancer Ile-379-Met ATT to ATG	ATGCTCAGAGAATCCTAGAGATACTGAAGATGTTCTTGGAT AACACTAAATAGCAGCATTGAGAAAGTTAATGAGTGGTTTTCC AGAAGTGATGAACTGTTAGGTTCTGATGACTCACAT	709

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGTGAGTCATCAGAACCTAACAGTTCATCACTTCTGGAAAAC CACTCATTAACCTTTCTGAATGCTGCTATTTAGTGTTATCCAAG GAACATCTTCAGTATCTCTAGGATTCTCTGAGCAT	710
	AGCAGCATTCAGAAAAGT	711
	ACTTTCTGAATGCTGCT	712
Breast Cancer Glu-421-Gly GAA to GGA	GGGAGTCTGAATCAAATGCCAAAGTAGCTGATGTATTGGACG TTCTAAATGAGGTAGATGAATATTCTGGTTCTTCAGAGAAAAT AGACTTACTGGCCAGTGATCCTCATGAGGCTTTAAT	713
	ATTAAAGCCTCATGAGGATCACTGGCCAGTAAGTCTATTTTCT CTGAAGAACCAGAATATTCATCTACCTCATTTAGAACGTCCAA TACATCAGCTACTTTGGCATTGATTGAGACTCCC	714
	GGTAGATGAATATTCTG	715
	CAGAATATTCATCTACC	716
Breast Cancer Phe-461-Leu TTT to CTT	ATATGTAAAAGTGAAAGAGTTCCTCCAAATCAGTAGAGAGTA ATATTGAAGACAAAATAATTTGGGAAAACCTATCGGAAGAAGG CAAGCCTCCCCAACTTAAGCCATGTAAGTGAATATC	717
	GATTTTCAGTTACATGGCTTAAGTTGGGGAGGCTTGCCTTCT TCCGATAGGTTTTCCCAAATATTTTGTCTTCAATATTACTCTCT ACTGATTTGGAGTGAAGTCTTTCACTTTTACATAT	718
	ACAAAATAATTTGGGAAA	719
	TTTCCCAAATATTTTGT	720
Breast Cancer Tyr-465-Leu TAT to GAT	GAAAGAGTTCCTCCAAATCAGTAGAGAGTAATATTGAAGAC AAAATATTTGGGAAAACCTATCGGAAGAAGGCAAGCCTCCCC AACTTAAGCCATGTAAGTGAATCTAATTATAGGAG	721
	CTCCTATAATTAGATTTTCAGTTACATGGCTTAAGTTGGGGAG GCTTGCCTTCTTCCGATAGGTTTTCCCAAATATTTTGTCTTCA ATATTACTCTCTACTGATTTGGAGTGAAGTCTTTC	722
	GGAAAACCTATCGGAAG	723
	CTTCCGATAGGTTTTCC	724
Breast Cancer Gly-484-Stop GGA to TGA	ACCTATCGGAAGAAGGCAAGCCTCCCCAACTTAAGCCATGTA ACTGAAAATCTAATTATAGGAGCATTTGTTACTGAGCCACAGA TAATACAAGAGCGTCCCCTCACAAATAAATTAAAGC	725
	GCTTTAATTTATTTGTGAGGGGACGCTCTTGTATTATCTGTGG CTCAGTAACAAATGCTCCTATAATTAGATTTTCAGTTACATGG CTTAAGTTGGGGAGGCTTGCCTTCTTCCGATAGGT	726

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAATTATAGGAGCATT	727
	AAATGCTCCTATAATTA	728
Breast Cancer Arg-507-Ile AGA to ATA	TTACTGAGCCACAGATAATACAAGAGCGTCCCCTCACAAATA AATTAAAGCGTAAAAGGAGACCTACATCAGGCCTTCATCCTG AGGATTTTATCAAGAAAGCAGATTTGGCAGTTCAAAA	729
	TTTTGAACTGCCAAATCTGCTTTCTTGATAAAATCCTCAGGAT GAAGGCCTGATGTAGGTCTCCTTTTACGCTTTAATTTATTTGT GAGGGGACGCTCTTGATTATCTGTGGCTCAGTAA	730
	TAAAAGGAGACCTACAT	731
	ATGTAGGTCTCCTTTTA	732
Breast Cancer Ser-510-Stop TCA to TGA	CACAGATAATACAAGAGCGTCCCCTCACAAATAAATTAAAGC GTAAAAGGAGACCTACATCAGGCCTTCATCCTGAGGATTTTA TCAAGAAAGCAGATTTGGCAGTTCAAAGACTCCTGA	733
	TCAGGAGTCTTTTGAAGTCCAAATCTGCTTTCTTGATAAAAT CCTCAGGATGAAGGCCTGATGTAGGTCTCCTTTTACGCTTTA ATTTATTTGTGAGGGGACGCTCTTGATTATCTGTG	734
	ACCTACATCAGGCCTTC	735
	GAAGGCCTGATGTAGGT	736
Breast Cancer Gln-526-Stop CAA to TAA	AGGAGACCTACATCAGGCCTTCATCCTGAGGATTTTATCAAG AAAGCAGATTTGGCAGTTCAAAGACTCCTGAAATGATAAATC AGGGAACCTAACCAACGGAGCAGAATGGTCAAGTGA	737
	TCACTTGACCATCTGCTCCGTTTGGTTAGTTCCCTGATTTAT CATTTCAGGAGTCTTTTGAAGTCCAAATCTGCTTTCTTGATA AAATCCTCAGGATGAAGGCCTGATGTAGGTCTCCT	738
	TGGCAGTTCAAAGACT	739
	AGTCTTTTGAAGTCCA	740
Breast Cancer Gln-541-Stop CAG to TAG	AGGAGACCTACATCAGGCCTTCATCCTGAGGATTTTATCAAG AAAGCAGATTTGGCAGTTCAAAGACTCCTGAAATGATAAATC AGGGAACCTAACCAACGGAGCAGAATGGTCAAGTGA	741
	TCACTTGACCATCTGCTCCGTTTGGTTAGTTCCCTGATTTAT CATTTCAGGAGTCTTTTGAAGTCCAAATCTGCTTTCTTGATA AAATCCTCAGGATGAAGGCCTGATGTAGGTCTCCT	742
	AAACGGAGCAGAATGGT	743
	ACCATTCTGCTCCGTTT	744

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Gly-552-Val GGT to GTT	TAAATCAGGGAACCTAACCAAACGGAGCAGAATGGTCAAGTGA TGAATATTACTAATAGTG G TCATGAGAATAAAACAAAAGGTGA TTCTATTGAGAATGAGAAAAATCCTAACCCAATAGA	745
	TCTATTGGGTTAGGATTTTTCTCATTCTGAATAGAATCACCTTT TGTTTTATTCTCATG A CCACTATTAGTAATATTCATCACTTGAC CATTCTGCTCCGTTTGGTTAGTTCCTGATTTA	746
	TAATAGTG G TCATGAGA	747
	TCTCATG A CCACTATTA	748
Breast Cancer Gln-563-Stop CAG to TAG	GGTCAAGTGATGAATATTACTAATAGTGGTCATGAGAATAAAA CAAAGGTGATTCTATT C AGAATGAGAAAAATCCTAACCCAAT AGAATCACTCGAAAAAGAATCTGCTTTCAAAACGA	749
	TCGTTTTGAAAGCAGATTCTTTTCGAGTGATTCTATTGGGTT AGGATTTTTCTCATTCT G AATAGAATCACCTTTTGTTTTATTCT CATGACCACTATTAGTAATATTCATCACTTGACC	750
	ATTCTATT C AGAATGAG	751
	CTCATTCT G AATAGAAT	752
Ovarian Cancer Lys-607-Stop AAA to TAA	ATAAGCAGCAGTATAAGCAATATGGAACCTCGAATTAAATATCC ACAATTCAAAGCACCT A AAAAAGAATAGGCTGAGGAGGAAGT CTTCTACCAGGCATATTCATGCGCTTGAACCTAGTAG	753
	CTACTAGTTCAAGCGCATGAATATGCCTGGTAGAAGACTTCC TCCTCAGCCTATTCTTTT I AGGTGCTTTTGAATTGTGGATATT TAATTCGAGTTCATATTGCTTATACTGCTGCTTAT	754
	AAGCACCT A AAAAAGAAT	755
	ATTCTTTT I AGGTGCTT	756
Breast Cancer Leu-639-Stop TTG to TAG	ATATTCATGCGCTTGAACCTAGTAGTCAGTAGAAATCTAAGCCC ACCTAATTGACTGAATT I GCAAATTGATAGTTGTTCTAGCAGT GAAGAGATAAAGAAAAAAGTACAACCAAATGCC	757
	GGCATTGTTGTACTTTTTTTCTTTATCTCTTCACTGCTAGA ACAATATCAATTTG A AATTCAGTACAATTAGGTGGGCTTAGA TTTCTACTGACTACTAGTTCAAGCGCATGAATAT	758
	TACTGAATT I GCAAATTG	759
	CAATTTG A AATTCAGTA	760
Breast Cancer Asp-693-Asn GAC to AAC	GAACCTGCAACTGGAGCCAAGAAGAGTAACAAGCCAAATGAA CAGACAAGTAAAAGACAT G ACAGCGATACTTTCCAGAGCTG AAGTTAACAATGCACCTGGTTCTTTTACTAAGTGTT	761

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AACACTTAGTAAAAGAACCAGGTGCATTTGTTAACTTCAGCTC TGGGAAAGTATCGCTGT <u>C</u> ATGTCTTTTACTTGTCTGTTCAATT GGCTTGTTACTCTTCTTGGCTCCAGTTGCAGGTTTC	762
	AAAGACAT <u>G</u> ACAGCGAT	763
	ATCGCTGT <u>C</u> ATGTCTTT	764
Ovarian Cancer Glu-720-Stop GAA to TAA	CTGAAGTTAACAAATGCACCTGGTTCTTTTACTAAGTGTTC ATACCAGTGAACCTTAAAG <u>G</u> AATTTGTCAATCCTAGCCTTCCAAG AGAAGAAAAAGAAGAGAACTAGAAACAGTTAAAG	765
	CTTTAACTGTTTCTAGTTTCTCTTCTTTTCTTCTCTTGAAGG CTAGGATTGACAAATT <u>C</u> TTTAAGTTCACTGGTATTTGAACACT TAGTAAAGAACCAGGTGCATTTGTTAACTTCAG	766
	AACTTAAAG <u>G</u> AATTTGTC	767
	GACAAATT <u>C</u> TTTAAGTT	768
Breast Cancer Glu-755-Stop GAA to TAA	CTAGAAACAGTTAAAGTGTCTAATAATGCTGAAGACCCCAA GATCTCATGTAAAGTGGAGAAAGGGTTTTGCAAACCTGAAAGA TCTGTAGAGAGTAGCAGTATTTTATTGGTACCTGGTA	769
	TACCAGGTACCAATGAAATACTGCTACTCTCTACAGATCTTTC AGTTTGCAAACCCCTTT <u>C</u> TCCACTTAACATGAGATCTTTGGGG TCTTCAGCATTATTAGACACTTTAACTGTTTCTAG	770
	TAAGTGGAGAAAGGGTT	771
	AACCCTTT <u>C</u> TCCACTTA	772
Breast Cancer Ser-770-Stop TCA to TAA	TCATGTTAAGTGGAGAAAGGGTTTTGCAAACCTGAAAGATCTG TAGAGAGTAGCAGTATTT <u>C</u> ATTGGTACCTGGTACTGATTATG GCACTCAGGAAAGTATCTCGTTACTGGAAGTTAGCAC	773
	GTGCTAACTTCCAGTAACGAGATACTTTCCTGAGTGCCATAA TCAGTACCAGGTACCAATGAAATACTGCTACTCTCTACAGAT CTTTCAGTTTGCAAACCCCTTTCTCCACTTAACATGA	774
	CAGTATTT <u>C</u> ATTGGTAC	775
	GTACCAATGAAATACTG	776
Breast Cancer Val-772-Ala GTA to GCA	TAAGTGGAGAAAGGGTTTTGCAAACCTGAAAGATCTGTAGAGA GTAGCAGTATTTTATTGGT <u>A</u> CTGGTACTGATTATGGCACTC AGGAAAGTATCTCGTTACTGGAAGTTAGCACTCTAGG	777
	CCTAGAGTGCTAACTTCCAGTAACGAGATACTTTCCTGAGTG CCATAATCAGTACCAGGT <u>A</u> CCAATGAAATACTGCTACTCTCTA CAGATCTTTCAGTTTGCAAACCCCTTTCTCCACTTA	778

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTCATTGGT <u>A</u> CTGGTA	779
	TACCAGGT <u>A</u> CCAATGAA	780
Breast Cancer Gln-780-Stop CAG to TAG	ACTGAAAGATCTGTAGAGAGTAGCAGTATTTTCATTGGTACCT GGTACTGATTATGGCACT <u>C</u> AGGAAAGTATCTCGTTACTGGAA GTTAGCACTCTAGGGAAGGCAAAAACAGAACCAAATA	781
	TATTTGGTTCTGTTTTTGCCTTCCCTAGAGTGCTAACTTCCAG TAACGAGATACTTTCTT <u>G</u> AGTGCCATAATCAGTACCAGGTAC CAATGAAATACTGCTACTCTCTACAGATCTTTCAGT	782
	ATGGCACT <u>C</u> AGGAAAGT	783
	ACTTTCCT <u>G</u> AGTGCCAT	784
Breast Cancer Glu-797-Stop GAA to TAA	TATGGCACTCAGGAAAGTATCTCGTTACTGGAAGTTAGCACT CTAGGGAAGGCAAAAACAG <u>A</u> ACCAAATAAATGTGTGAGTCAG TGTGCAGCATTTGAAAACCCCAAGGGACTAATTCATG	785
	CATGAATTAGTCCCTTGGGGTTTTCAAATGCTGCACACTGAC TCACACATTTATTTGGTT <u>C</u> TGTTTTTGCCTTCCCTAGAGTGCT AACTTCCAGTAACGAGATACTTTCTGAGTGCCATA	786
	CAAAAACAG <u>A</u> ACCAAAT	787
	ATTTGGTT <u>C</u> TGTTTTTG	788
Breast Cancer Lys-820-Glu AAA to GAA	AAATGTGTGAGTCAGTGTGCAGCATTTGAAAACCCCAAGGGA CTAATTCATGGTTGTTCC <u>A</u> AAGATAATAGAAATGACACAGAAG GCTTTAAGTATCCATTGGGACATGAAGTTAACCACA	789
	TGTGGTTAACTTCATGTCCCAATGGATACTTAAAGCCTTCTGT GTCATTTCTATTATCTTT <u>T</u> GGAACAACCATGAATTAGTCCCTTG GGGTTTTCAAATGCTGCACACTGACTCACACATTT	790
	GTTGTTCC <u>A</u> AAGATAAT	791
	ATTATCTTTGGAACAAC	792
Breast Cancer Thr-826-Lys ACA to AAA	CAGCATTTGAAAACCCCAAGGGACTAATTCATGGTTGTTCCA AAGATAATAGAAATGACAC <u>A</u> GGAAGGCTTTAAGTATCCATTGG GACATGAAGTTAACCACAGTCGGGAAACAAGCATAGA	793
	TCTATGCTTGTTTTCCCGACTGTGGTTAACTTCATGTCCCAATG GATACTTAAAGCCTTCT <u>G</u> TGTCATTTCTATTATCTTTGGAACA ACCATGAATTAGTCCCTTGGGGTTTTCAAATGCTG	794
	AAATGACAC <u>A</u> GGAAGGCT	795
	AGCCTTCT <u>G</u> TGTCATTT	796

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Arg-841-Trp CGG to TGG	GATAATAGAAATGACACAGAAGGCTTTAAGTATCCATTGGGA CATGAAGTTAACCACAGTGGGAAACAAGCATAGAAATGGAA GAAAGTGAAGTTGATGCTCAGTATTTGCAGAATACAT	797
	ATGTATTCTGCAAATACTGAGCATCAAGTTCACTTTCTTCCAT TTCTATGCTTGTTCCTGACTGTGGTTAACTTCATGTCCCAAT GGATACTTAAAGCCTTCTGTGTCATTTCTATTATC	798
	ACCACAGTGGGAAACA	799
	TGTTTCCCAGACTGTGGT	800
Breast Cancer Pro-871-Leu CCG to CTG	AACTTGATGCTCAGTATTTGCAGAATACATTCAAGGTTTCAA GCGCCAGTCATTTGCTCCGTTTTCAAATCCAGGAAATGCAGA AGAGGAATGTGCAACATTCTCTGCCCACTCTGGGTC	801
	GACCCAGAGTGGGCAGAGAATGTTGCACATTCCTCTTCTGCA TTTCCTGGATTTGAAAACGGAGCAAATGACTGGCGCTTTGAA ACCTTGAATGTATTCTGCAAATACTGAGCATCAAGTT	802
	ATTTGCTCCGTTTTCAA	803
	TTGAAAACGGAGCAAAT	804
Breast Cancer Leu-892-Ser TTA to TCA	TTTCAAATCCAGGAAATGCAGAAGAGGAATGTGCAACATTCT CTGCCCACTCTGGGTCTTAAAGAAACAAAGTCCAAAAGTCA CTTTTGAATGTGAACAAAAGGAAGAAATCAAGGAAA	805
	TTTCCTTGATTTTCTTCCTTTTGTTACATTCAAAGTGACTTT TGGACTTTGTTTCTTTAAGGACCCAGAGTGGGCAGAGAATGT TGCACATTCCTCTTCTGCATTTCTGGATTTGAAA	806
	TGGGTCCTTAAAGAAAC	807
	GTTTCTTTAAGGACCCA	808
Breast Cancer Glu-908-Stop GAA to TAA	CACTCTGGGTCTTAAAGAAACAAAGTCCAAAAGTCACTTTTG AATGTGAACAAAAGGAAAGAAATCAAGGAAAGAATGAGTCTA ATATCAAGCCTGTACAGACAGTTAATATCACTGCAG	809
	CTGCAGTGATATTAAGTGTCTGTACAGGCTTGATATTAGACTC ATTCTTTCCTTGATTTTCTTCCTTTTGTTACATTCAAAGTGA CTTTTGGACTTTGTTTCTTTAAGGACCCAGAGTG	810
	AAAAGGAAGAAATCAA	811
	TTGATTTTCTTCCTTTT	812
Breast Cancer Gly-960-Asp GGC to GAC	ATAATGCCAAATGTAGTATCAAAGGAGGCTCTAGGTTTTGTCT ATCATCTCAGTTCAGAGGCAACGAAACTGGACTCATTACTCC AAATAACATGGACTTTTACAAAACCCATATCGTAT	813

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATACGATATGGGTTTTGTAAAAGTCCATGTTTATTTGGAGTAA TGAGTCCAGTTTCGTTG <u>C</u> CTCTGAACTGAGATGATAGACAAA ACCTAGAGCCTCCTTTGATACTACATTTGGCATTAT	814
	GTTCAAGAG <u>G</u> CAACGAAA	815
	TTTCGTTG <u>C</u> CTCTGAAC	816
Breast Cancer Met-1008-Ile ATG to ATA	ATTTGTTAAACTAAATGTAAGAAAAATCTGCTAGAGGAAAAC TTTGAGGAACATTCAATGTCACCTGAAAGAGAAATGGGAAAT GAGAACATTCCAAGTACAGTGAGCACAATTAGCCGT	817
	ACGGCTAATTGTGCTCACTGTACTTGAATGTTCTCATTTCCC ATTTCTCTTTCAGGTGACATTGAATGTTCTCAAAGTTTTCT CTAGCAGATTTTCTTACATTTAGTTTAAACAAAT	818
	CATTCAATGTCACCTGA	819
	TCAGGTGACATTGAATG	820
Breast Cancer Thr-1025-Ile ACA to ATA	ACTTTGAGGAACATTCAATGTCACCTGAAAGAGAAATGGGAA ATGAGAACATTCCAAGTACAGTGAGCACAATTAGCCGTAATA ACATTAGAGAAAATGTTTTAAAGAAGCCAGCTCAAG	821
	CTTGAGCTGGCTTCTTTAAAAACATTTCTCTAATGTTATTACG GCTAATTGTGCTCACTGTACTTGAATGTTCTCATTTCCCATT TCTCTTTCAGGTGACATTGAATGTTCTCAAAGT	822
	TCCAAGTACAGTGAGCA	823
	TGCTCACTGTACTTGA	824
Breast Cancer Glu-1038-Gly GAA to GGA	ACATTCCAAGTACAGTGAGCACAATTAGCCGTAATAACATTAG AGAAAATGTTTTTAAAGAGCCAGCTCAAGCAATATTAATGAA GTAGGTTCCAGTACTAATGAAGTGGGCTCCAGTAT	825
	ATACTGGAGCCCACTTCATTAGTACTGGAACCTACTTCATTAA TATTGCTTGAGCTGGCTTCTTTAAAAACATTTCTCTAATGTTA TTACGGCTAATTGTGCTCACTGTACTTGAATGT	826
	TTTTAAAGAGCCAGCT	827
	AGCTGGCTTCTTTAAAA	828
Breast Cancer Ser-1040-Asn AGC to AAC	CAAGTACAGTGAGCACAATTAGCCGTAATAACATTAGAGAAA ATGTTTTTAAAGAAGCCAGCTCAAGCAATATTAATGAAGTAGG TTCCAGTACTAATGAAGTGGGCTCCAGTATTAATGA	829
	TCATTAATACTGGAGCCCACTTCATTAGTACTGGAACCTACTT CATTAATATTGCTTGAGCTGGCTTCTTTAAAAACATTTCTCTA ATGTTATTACGGCTAATTGTGCTCACTGTACTTG	830

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGAAGCCAGCTCAAGCA	831
	TGCTTGAGCTGGCTTCT	832
Breast Cancer Val-1047-Ala GTA to GCA	GCCGTAATAACATTAGAGAAAATGTTTTAAAGAAGCCAGCTC AAGCAATATTAATGAAGTAGGTTCCAGTACTAATGAAGTGGG CTCCAGTATTAATGAAATAGGTTCCAGTGATGAAAA	833
	TTTTCATCACTGGAACCTATTTTCAATACTGGAGCCCACTT CATTAGTACTGGAACCTACTTCATTAATATTGCTTGAGCTGGC TTCTTTAAAACATTTTCTCTAATGTTATTACGGC	834
	TAATGAAGTAGGTTCCA	835
	TGGAACCTACTTCATTA	836
Breast Cancer Leu-1080-Stop TTG to TAG	AAATAGGTTCCAGTGATGAAAACATTCAAGCAGAACTAGGTA GAAACAGAGGGCCAAAATTGAATGCTATGCTTAGATTAGGGG TTTTGCAACCTGAGGTCTATAAACAAAGTCTTCCTGG	837
	CCAGGAAGACTTTGTTTATAGACCTCAGGTTGCAAACCCCT AATCTAAGCATAGCATTCAATTTTGGCCCTCTGTTTCTACCTA GTTCTGCTTGAATGTTTTCATCACTGGAACCTATTT	838
	GCCAAAATTGAATGCTA	839
	TAGCATTCAATTTTGGC	840
Breast Cancer Leu-1086-Stop TTA to TGA	AAAACATTCAAGCAGAACTAGGTAGAAACAGAGGGCCAAAAT TGAATGCTATGCTTAGATTAGGGGTTTTGCAACCTGAGGTCT ATAAACAAAGTCTTCCTGGAAGTAATTGTAAGCATCC	841
	GGATGCTTACAATTACTTCCAGGAAGACTTTGTTTATAGACCT CAGGTTGCAAACCCCTAATCTAAGCATAGCATTCAATTTG GCCCTCTGTTTCTACCTAGTTCTGCTTGAATGTTTT	842
	GCTTAGATTAGGGGTTT	843
	AAACCCCTAATCTAAGC	844
Breast Cancer Ser-1130-Stop TCA to TGA	AGCAAGAATATGAAGAAGTAGTTCAGACTGTTAATACAGATTT CTCTCCATATCTGATTTAGATAAATTAGAACAGCCTATGGGA AGTAGTCATGCATCTCAGGTTTGTTCTGAGACACC	845
	GGTGTCTCAGAACAAACCTGAGATGCATGACTACTTCCATA GGCTGTTCTAAGTTATCTGAAATCAGATATGGAGAGAAATCT GTATTAACAGTCTGAACACTTCTTCATATTCTTGCT	846
	TCTGATTTAGATAACT	847
	AGTTATCTGAAATCAGA	848

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Lys-1183-Arg AAA to AGA	CTAGTTTTGCTGAAAATGACATTAAGGAAAGTTCTGCTGTTTT TAGCAAAAGCGTCCAGAAAGGAGAGCTTAGCAGGAGTCCTA GCCCTTTCACCCATACACATTTGGCTCAGGGTTACCG	849
	CGGTAACCCTGAGCCAAATGTGTATGGGTGAAAGGGCTAGG ACTCCTGCTAAGCTCTCCTTTCTGGACGCTTTTGCTAAAAACA GCAGAACTTTCCTTAATGTCATTTTCAGCAAACTAG	850
	CGTCCAGAAAGGAGAGC	851
	GCTCTCCTTTCTGGACG	852
Breast Cancer Gln-1200-Stop CAG to TAG	AGCGTCCAGAAAGGAGAGCTTAGCAGGAGTCCTAGCCCTTT CACCCATACACATTTGGCTCAGGGTTACCGAAGAGGGGCCA AGAAATTAGAGTCCTCAGAAGAGAACTTATCTAGTGAGG	853
	CCTCACTAGATAAGTTCTCTTCTGAGGACTCTAATTTCTTGGC CCCTCTTCGGTAACCCTGAGCCAAATGTGTATGGGTGAAAGG GCTAGGACTCCTGCTAAGCTCTCCTTTCTGGACGCT	854
	ATTTGGCTCAGGGTTAC	855
	GTAACCCTGAGCCAAAT	856
Breast Cancer Arg-1203-Stop CGA to TGA	AAAGGAGAGCTTAGCAGGAGTCCTAGCCCTTTCACCCATACA CATTTGGCTCAGGGTTACCGAAGAGGGGCCAAGAAATTAGA GTCCTCAGAAGAGAACTTATCTAGTGAGGATGAAGAGC	857
	GCTCTTCATCCTCACTAGATAAGTTCTCTTCTGAGGACTCTAA TTTCTTGGCCCCCTCTTCGTAACCCTGAGCCAAATGTGTATG GGTGAAAGGGCTAGGACTCCTGCTAAGCTCTCCTTT	858
	AGGGTTACCGAAGAGGG	859
	CCCTCTTCGGTAACCCT	860
Breast Cancer Glu-1214-Stop GAG to TAG	ACCCATACACATTTGGCTCAGGGTTACCGAAGAGGGGCCAA GAAATTAGAGTCCTCAGAAAGAGAACTTATCTAGTGAGGATGA AGAGCTTCCCTGCTTCCAACACTTGTTATTTGGTAAAG	861
	CTTTACCAAATAACAAGTGTGGAAGCAGGGAAGCTCTTCAT CCTCACTAGATAAGTTCTCTTCTGAGGACTCTAATTTCTTGGC CCCTCTTCGGTAACCCTGAGCCAAATGTGTATGGGT	862
	CCTCAGAAAGAGAACTTA	863
	TAAGTTCTCTTCTGAGG	864
Breast Cancer Glu-1219-Asp GAG to GAC	TCAGGGTTACCGAAGAGGGGCCAAGAAATTAGAGTCCTCAG AAGAGAACTTATCTAGTGAGGATGAAGAGCTTCCCTGCTTCC AACACTTGTTATTTGGTAAAGTAAACAATATACCTTCT	865

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGAAGGTATATTGTTTACTTTACCAAATAACAAGTGTTGGAAG CAGGGAAGCTCTTCATCCTCACTAGATAAGTTCTCTTCTGAG GACTCTAATTTCTTGGCCCCTCTTCGGTAACCCTGA	866
	TCTAGTGAGGATGAAGA	867
	TCTTCATCCTCACTAGA	868
Breast Cancer Glu-1221-Stop GAA to TAA	GGTTACCGAAGAGGGGCCAAGAAATTAGAGTCCTCAGAAGA GAACTTATCTAGTGAGGATGAAGAGCTTCCCTGCTTCCAACA CTTGTTATTTGGTAAAGTAAACAATATACCTTCTCAGT	869
	ACTGAGAAGGTATATTGTTTACTTTACCAAATAACAAGTGTTG GAAGCAGGGAAGCTCTTCATCCTCACTAGATAAGTTCTCTTC TGAGGACTCTAATTTCTTGGCCCCTCTTCGGTAACC	870
	GTGAGGATGAAGAGCTT	871
	AAGCTCTTCATCCTCAC	872
Breast Cancer Glu-1250-Stop GAG to TAG	TTATTTGGTAAAGTAAACAATATACCTTCTCAGTCTACTAGGC ATAGCACCGTTGCTACCGAGTGTCTGTCTAAGAACACAGAGG AGAATTTATTATCATTGAAGAATAGCTTAAATGACT	873
	AGTCATTTAAGCTATTCTTCAATGATAATAAATTCTCCTCTGTG TTCTTAGACAGACACTCGGTAGCAACGGTGCTATGCCTAGTA GACTGAGAAGGTATATTGTTTACTTTACCAAATAA	874
	TTGCTACCGAGTGTCTG	875
	CAGACACTCGGTAGCAA	876
Breast Cancer Ser-1262-Stop TCA to TAA	CTAGGCATAGCACCGTTGCTACCGAGTGTCTGTCTAAGAACA CAGAGGAGAATTTATTATCATTGAAGAATAGCTTAAATGACTG CAGTAACCAGGTAATATTGGCAAAGGCATCTCAGGA	877
	TCCTGAGATGCCTTTGCCAATATTACCTGGTTACTGCAGTCAT TTAAGCTATTCTTCAATGATAATAAATTCTCCTCTGTGTTCTTA GACAGACACTCGGTAGCAACGGTGCTATGCCTAG	878
	TTTATTATCATTGAAGA	879
	TCTTCAATGATAATAAA	880
Breast Cancer Gln-1281-Stop CAG to TAG	TTATCATTGAAGAATAGCTTAAATGACTGCAGTAACCAGGTAA TATTGGCAAAGGCATCTCAGGAACATCACCTTAGTGAGGAAA CAAAATGTTCTGCTAGCTTGTTTCTTCACAGTGCA	881
	TGCACTGTGAAGAAAACAAGCTAGCAGAACATTTTGTTCCTC ACTAAGGTGATGTTTCTGAGATGCCTTTGCCAATATTACCTG GTTACTGCAGTCATTTAAGCTATTCTTCAATGATAA	882

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGGCATCTCAGGAACAT	883
	ATGTTCCCTGAGATGCCT	884
Breast Cancer Gln-1313-Stop CAG to TAG	GCTAGCTTGTTTTCTTCACAGTGCAGTGAATTGGAAGACTTG ACTGCAAATACAAACACCCAGGATCCTTTCTTGATTGGTTCTT CCAAACAAATGAGGCATCAGTCTGAAAGCCAGGGAG	885
	CTCCCTGGCTTTCAGACTGATGCCTCATTTGTTTGGAAGAAC CAATCAAGAAAGGATCCTGGGTGTTTGTATTTGCAGTCAAGT CTTCCAATTCAGTGCAGTGTGAAGAAAACAAGCTAGC	886
	CAAACACCCAGGATCCT	887
	AGGATCCTGGGTGTTTG	888
Breast Cancer Ile-1318-Val ATT to GTT	TCACAGTGCAGTGAATTGGAAGACTTGACTGCAAATACAAAC ACCCAGGATCCTTTCTTGATTGGTTCTTCCAAACAAATGAGG CATCAGTCTGAAAGCCAGGGAGTTGGTCTGAGTGACA	889
	TGTCAGTCAAGCAACTCCCTGGCTTTCAGACTGATGCCTCA TTTGTGTTGGAAGAACAATCAAGAAAGGATCCTGGGTGTTTG TATTTGCAGTCAAGTCTTCCAATTCAGTGCAGTGTGA	890
	CTTTCTTGATTGGTTCT	891
	AGAACCAATCAAGAAAG	892
Breast Cancer Gln-1323-Stop CAA to TAA	TTGGAAGACTTGACTGCAAATACAAACACCCAGGATCCTTTC TTGATTGGTTCTTCCAAACAAATGAGGCATCAGTCTGAAAGC CAGGGAGTTGGTCTGAGTGACAAGGAATTGGTTTCAG	893
	CTGAAACCAATTCCTTGCACTCAGACCAACTCCCTGGCTTT CAGACTGATGCCTCATTTGTTTGGAAGAACAATCAAGAAAG GATCCTGGGTGTTTGTATTTGCAGTCAAGTCTTCCAA	894
	CTTCCAAACAAATGAGG	895
	CCTCATTTGTTTGGAAG	896
Breast Cancer Arg-1347-Gly AGA to GGA	CAGTCTGAAAGCCAGGGAGTTGGTCTGAGTGACAAGGAATT GGTTTCAGATGATGAAGAAAGAGGAACGGGCTTGGAAGAAA ATAATCAAGAAGAGCAAAGCATGGATTCAAACCTTAGGTA	897
	TACCTAAGTTTGAATCCATGCTTTGCTCTTCTTGATTATTTCT TCCAAGCCCGTTCTCTTCTTCATCATCTGAAACCAATTCCT TGTCAGTCAAGCAACTCCCTGGCTTTCAGACTG	898
	ATGAAGAAAGAGGAACG	899
	CGTTCCTCTTCTTCAT	900

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Gln-1395-Stop CAG to TAG	GAAACAAGCGTCTCTGAAGACTGCTCAGGGCTATCCTCTCAG AGTGACATTTTAACCACTCAGGTAAAAAGCGTGTGTGTGTGT GCACATGCGTGTGTGTGGTGTCCCTTGCATTCACTAG	901
	CTACTGAATGCAAAGGACACCACACACACGCATGTGCACACA CACACACGCTTTTTACCTGAGTGGTTAAAATGTCACTCTGAG AGGATAGCCCTGAGCAGTCTTCAGAGACGCTTGTTTC	902
	TAACCACTCAGGTAAAA	903
	TTTTACCTGAGTGGTTA	904
Breast Cancer Gln-1408-Stop CAG to TAG	TGGTGCCATTTATCGTTTTTGAAGCAGAGGGATACCATGCAA CATAACCTGATAAAGCTCCAGCAGGAAATGGCTGAACTAGAA GCTGTGTTAGAACAGCATGGGAGCCAGCCTTCTAACA	905
	TGTTAGAAGGCTGGCTCCCATGCTGTTCTAACACAGCTTCTA GTTTCAGCCATTTCTGCTGGAGCTTTATCAGGTTATGTTGCAT GGTATCCCTCTGCTTCAAAAACGATAAATGGCACCA	906
	TAAAGCTCCAGCAGGAA	907
	TTCTGCTGGAGCTTTA	908
Breast Cancer Arg-1443-Gly CGA to GGA	AGCCAGCCTTCTAACAGCTACCCTTCCATCATAAGTGACTCT TCTGCCCTTGAGGACCTGCAGAAATCCAGAACAAAGCACATCA GAAAAAGGTGTGTATTGTTGCCAAACACTGATATCT	909
Arg-1443-Stop CGA to TGA	AGATATCAGTGTTTGGCCAACAATACACACCTTTTTCTGATGT GCTTTGTTCTGGATTTCGAGGTCCTCAAGGGCAGAAGAGTC ACTTATGATGGAAGGGTAGCTGTTAGAAGGCTGGCT	910
	AGGACCTGCAGAAATCCA	911
	TGGATTTCCGAGGTCCT	912
Breast Cancer Ser-1512-Ile AGT to ATT	CAGAATAGAACTACCCATCTCAAGAGGAGCTCATTAAAGTT GTTGATGTGGAGGAGCAACAGCTGGAAGAGTCTGGGCCACA CGATTTGACGGAACATCTTACTTGCCAAGGCAAGATC	913
	GATCTTGCCCTTGCAAGTAAGATGTTTCCGTCAAATCGTGTG GCCCAGACTCTTCCAGCTGTTGCTCCTCCACATCAACAACCT TAATGAGCTCCTCTGAGATGGGTAGTTTCTATTCTG	914
	AGGAGCAACAGCTGGAA	915
	TTCCAGCTGTTGCTCCT	916
Breast Cancer Gln-1538-Stop CAG to TAG	ATCTTTCTAGGTCATCCCCTTCTAAATGCCCATCATTAGATGA TAGGTGGTACATGCACAGTTGCTCTGGGAGTCTTCAGAATAG AAACTACCCATCTCAAGAGGAGCTCATTAAAGGTTGT	917

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ACAACCTTAATGAGCTCCTCTTGAGATGGGTAGTTTCTATTCT GAAGACTCCCAGAGCAACTGTGCATGTACCACCTATCATCTA ATGATGGGCATTTAGAAGGGGATGACCTAGAAAGAT	918
	CATGCACAGTTGCTCTG	919
	CAGAGCAACTGTGCATG	920
Breast Cancer Glu-1541-Stop GAG to TAG	CAGAATAGAACTACCCATCTCAAGAGGAGCTCATTAAAGGTT GTTGATGTGGAGGAGCAACAGCTGGAAGAGTCTGGGCCACA CGATTTGACGGAACATCTTACTTGCCAAGGCAAGATC	921
	GATCTTGCCTTGGCAAGTAAGATGTTTCCGTCAAATCGTGTG GCCCAGACTCTTCCAGCTGTTGCTCCTCCACATCAACAACCT TAATGAGCTCCTCTTGAGATGGGTAGTTTCTATTCTG	922
	AGGAGCAACAGCTGGAA	923
	TTCCAGCTGTTGCTCCT	924
Breast Cancer Thr-1561-Ile ACC to ATC	AACTACCCATCTCAAGAGGAGCTCATTAAAGGTTGTTGATGTG GAGGAGCAACAGCTGGAAGAGTCTGGGCCACACGATTTGAC GGAAACATCTTACTTGCCAAGGCAAGATCTAGGTAATA	925
	TATTACCTAGATCTTGCCTTGGCAAGTAAGATGTTTCCGTCAA ATCGTGTGGCCAGACTCTTCCAGCTGTTGCTCCTCCACATC AACAACCTTAATGAGCTCCTCTTGAGATGGGTAGTT	926
	AGCTGGAAGAGTCTGGG	927
	CCCAGACTCTTCCAGCT	928
Breast Cancer Tyr-1563-Stop TAC to TAG	TTTGTAATTCAACATTCATCGTTGTGTAAATTAACCTTCTCCCA TTCTTTTCAGAGGGAACCCCTTACCTGGAATCTGGAATCAGC CTCTTCTCTGATGACCCTGAATCTGATCCTTCTGA	929
	TCAGAAGGATCAGATTCAGGGTCATCAGAGAAGAGGCTGATT CCAGATTCCAGGTAAGGGGTTCCCTCTGAAAGGAATGGGAG AAGTTTAATTTACACAACGATGAATGTTGAATTACAAA	930
	AGAGGGAACCCCTTACC	931
	GGTAAGGGGTTCCCTCT	932
Breast Cancer Leu-1564-Pro CTG to CCG	CAACATTCATCGTTGTGTAAATTAACCTTCTCCATTCTTTTC AGAGGGAACCCCTTACCTGGAATCTGGAATCAGCCTCTTCTC TGATGACCCTGAATCTGATCCTTCTGAAGACAGAGC	933
	GCTCTGTCTTCAGAAGGATCAGATTCAGGGTCATCAGAGAAG AGGCTGATTCCAGATTCCAGGTAAGGGGTTCCCTCTGAAAG GAATGGGAGAAGTTTAATTTACACAACGATGAATGTTG	934

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CCCTTACCT <u>I</u> GGAATCTG	935
	CAGATTCC <u>A</u> GGTAAGGG	936
Breast Cancer Gln-1604-Stop CAA to TAA	GCCCCAGAGTCAGCTCGTGTGGCAACATACCATCTTCAACC TCTGCATTGAAAGTTCCCC <u>C</u> AATTGAAAGTTGCAGAATCTGCC CAGAGTCCAGCTGCTGCTCATACTACTGATACTGCTG	937
	CAGCAGTATCAGTAGTATGAGCAGCAGCTGGACTCTGGGCA GATTCTGCAACTTTCAATT <u>G</u> GGGAACTTTCAATGCAGAGGTT GAAGATGGTATGTTGCCAACACGAGCTGACTCTGGGGC	938
	AAGTTCCCC <u>C</u> AATTGAAA	939
	TTTCAATT <u>G</u> GGGAACTT	940
Breast Cancer Lys-1606-Glu AAA to GAA	GAGTCAGCTCGTGTGGCAACATACCATCTTCAACCTCTGCA TTGAAAGTTCCCCAATTG <u>A</u> AAGTTGCAGAATCTGCCCAGAGT CCAGCTGCTGCTCATACTACTGATACTGCTGGGTATA	941
	TATACCCAGCAGTATCAGTAGTATGAGCAGCAGCTGGACTCT GGGCAGATTCTGCAACTTT <u>T</u> CAATTGGGAACTTTCAATGCAG AGGTTGAAGATGGTATGTTGCCAACACGAGCTGACTC	942
	CCCAATTG <u>A</u> AAGTTGCA	943
	TGCAACTTT <u>T</u> CAATTGGG	944
Breast Cancer Met-1628-Thr ATG to ACG	CAGAATCTGCCCAGAGTCCAGCTGCTGCTCATACTACTGATA CTGCTGGGTATAATGCA <u>T</u> GGAAGAAAGTGTGAGCAGGGAG AAGCCAGAATTGACAGCTTCAACAGAAAGGGTCAACAA	945
	TTGTTGACCCTTTCTGTTGAAGCTGTCAATTCTGGCTTCTCCC TGCTCACACTTTCTTCC <u>A</u> TTGCATTATACCCAGCAGTATCAGT AGTATGAGCAGCAGCTGGACTCTGGGCAGATTCTG	946
	TAATGCAAT <u>T</u> GGAAGAAA	947
	TTTCTTCC <u>A</u> TTGCATTA	948
Breast Cancer Met-1628-Val ATG to GTG	GCAGAATCTGCCCAGAGTCCAGCTGCTGCTCATACTACTGAT ACTGCTGGGTATAATGCA <u>A</u> TGGAAGAAAGTGTGAGCAGGGA GAAGCCAGAATTGACAGCTTCAACAGAAAGGGTCAACA	949
	TGTTGACCCTTTCTGTTGAAGCTGTCAATTCTGGCTTCTCCCT GCTCACACTTTCTTCC <u>A</u> TTGCATTATACCCAGCAGTATCAGTA GTATGAGCAGCAGCTGGACTCTGGGCAGATTCTGC	950
	ATAATGCA <u>A</u> TGGAAGAA	951

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTCTTCCATTGCATTAT	952
Breast Cancer Pro-1637-Leu CCA to CTA	CTCATACTACTGATACTGCTGGGTATAATGCAATGGAAGAAA GTGTGAGCAGGGAGAAGCCAGAATTGACAGCTTCAACAGAA AGGGTCAACAAAAGAATGTCCATGGTGGTGTCTGGCCT	953
	AGGCCAGACACCACCATGGACATTCTTTTGTGACCCTTTCT GTTGAAGCTGTCAATTCTGGCTTCTCCCTGCTCACACTTTCTT CCATTGCATTATACCCAGCAGTATCAGTAGTATGAG	954
	GGAGAAGCCAGAATTGA	955
	TCAATTCTGGCTTCTCC	956
Breast Cancer Met-1652-Ile ATG to ATA	GAGCAGGGAGAAGCCAGAATTGACAGCTTCAACAGAAAGGG TCAACAAAAGAATGTCCATGGTGGTGTCTGGCCTGACCCAG AAGAATTTGTGAGTGTATCCATATGTATCTCCCTAATG	957
	CATTAGGGAGATACATATGGATACACTCACAAATTCTTCTGG GGTCAGGCCAGACACCACCATGGACATTCTTTTGTGACCCT TTCTGTTGAAGCTGTCAATTCTGGCTTCTCCCTGCTC	958
	ATGTCCATGGTGGTGTG	959
	GACACCACCATGGACAT	960
Breast Cancer Glu-1694-Stop GAG to TAG	CACTTCCTGATTTTGTTCCTCAACTTCTAATCCTTTGAGTGTTTT TCATTCTGCAGATGCTGAGTTTGTGTGTGAACGGACACTGAA ATATTTTCTAGGAATTGCGGGAGGAAAATGGGTAG	961
	CTACCCATTTTCTCCCGCAATTCCTAGAAAATATTTCAAGTGT CCGTTACACACAAACTCAGCATCTGCAGAATGAAAAACACT CAAAGGATTAGAAGTTGAAAACAAATCAGGAAGTG	962
	CAGATGCTGAGTTTGTG	963
	CACAAACTCAGCATCTG	964
Breast Cancer Gly-1706-Glu GGA to GAA	GTGTTTTTCATTCTGCAGATGCTGAGTTTGTGTGTGAACGGA CACTGAAATATTTCTAGGAATTGCGGGAGGAAAATGGGTAG TTAGCTATTTCTGTAAGTATAATACTATTTCTCCCCT	965
	AGGGGAGAAATAGTATTATACTTACAGAAATAGCTAACTACCC ATTTTCTCCCGCAATTCCTAGAAAATATTTCAAGTGTCCGTTT ACACACAAACTCAGCATCTGCAGAATGAAAAACAC	966
	TTTTCTAGGAATTGCGG	967
	CCGCAATTCCTAGAAAA	968

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Ala-1708-Glu GCG to GAG	TTCATTCTGCAGATGCTGAGTTTGTGTGTGAACGGACACTGA AATATTTTCTAGGAATTGCGGGAGGAAAATGGGTAGTTAGCT ATTTCTGTAAGTATAATACTATTTCTCCCCTCCTCCC	969
	GGGAGGAGGGGAGAAATAGTATTATACTTACAGAAATAGCTA ACTACCCATTTTCTCCC <u>G</u> CAATTCCTAGAAAATATTTCAAGTG TCCGTTACACACAAACTCAGCATCTGCAGAATGAA	970
	AGGAATTGCGGGAGGAA	971
	TTCTCCC <u>G</u> CAATTCCT	972
Breast Cancer Val-1713-Ala GTA to GCA	CTGAGTTTGTGTGTGAACGGACACTGAAATATTTTCTAGGAAT TGCGGGAGGAAAATGGGTAGTTAGCTATTTCTGTAAGTATAA TACTATTTCTCCCCTCCTCCCTTTAACACCTCAGAA	973
	TTCTGAGGTGTTAAAGGGAGGAGGGGAGAAATAGTATTATAC TTACAGAAATAGCTAACTACCCATTTTCTCCCGCAATTCCTA GAAAATATTTCAAGTGCCGTTACACACAAACTCAG	974
	AAAATGGGTAGTTAGCT	975
	AGCTAACTACCCATTTT	976
Breast Cancer Trp-1718-Stop TGG to TAG	AACGGACACTGAAATATTTTCTAGGAATTGCGGGAGGAAAAT GGGTAGTTAGCTATTTCTGTAAGTATAATACTATTTCTCCCCT CCTCCCTTTAACACCTCAGAATTGCATTTTACACC	977
	GGTGTA AAAATGCAATTCCTGAGGTGTTAAAGGGAGGAGGGG AGAAATAGTATTATACTTACAGAAATAGCTAACTACCCATTTTC CTCCCGCAATTCCTAGAAAATATTTCAAGTGCCGTT	978
	CTATTTCTGTAAGTATA	979
	TATACTTACAGAAATAG	980
Breast Cancer Glu-1725-Stop GAA to TAA	TTCTGCTGTATGTAACCTGTCTTTTCTATGATCTCTTTAGGGG TGACCCAGTCTATTAAGGAAAGAAAAATGCTGAATGAGGTAA GTACTTGATGTTACAACTAACCAGAGATATTCATT	981
	AATGAATATCTCTGGTTAGTTTGTAACATCAAGTACTTACCTC ATTCAGCATTTTCTTTCTTTAATAGACTGGGTCACCCCTAAA GAGATCATAGAAAAGACAGGTTACATACAGCAGAA	982
	CTATTAAGGAAAGAAAA	983
	TTTTCTTTCTTTAATAG	984
Breast Cancer Lys-1727-Stop AAA to TAA	TGTATGTAACCTGTCTTTTCTATGATCTCTTTAGGGGTGACCC AGTCTATTAAGAAAGAAAATGCTGAATGAGGTAAGTACTTG ATGTTACAACTAACCAGAGATATTCATTCAGTCA	985

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TGACTGAATGAATATCTCTGGTTAGTTTGTAAATCAAGTACT TACCTCATTGAGCATTITCTTTCTTTAATAGACTGGGTCACC CCTAAAGAGATCATAGAAAAGACAGGTTACATACA	986
	AAGAAAGAA A AAATGCTG	987
	CAGCATTITCTTTCTT	988
Breast Cancer Pro-1749-Arg CCA to CGA	TCTTTCAGCATGATTTTGAAGTCAGAGGAGATGTGGTCAATG GAAGAAACCACCAAGGTCC C AAAGCGAGCAAGAGAATCCCAG GACAGAAAGGTAAAGCTCCCTCCCTCAAGTTGACAAAA	989
	TTTTGTCAACTTGAGGGAGGGAGCTTTACCTTTCTGTCCTGG GATTCTCTTGCTCGCTTT G GACCTTGGTGGTTTCTTCCATTGA CCACATCTCCTCTGACTTCAAAATCATGCTGAAAGA	990
	CCAAGGTCC C AAAGCGAG	991
	CTCGCTTT G GACCTTGG	992
Breast Cancer Arg-1751-Stop CGA to TGA	CAGCATGATTTTGAAGTCAGAGGAGATGTGGTCAATGGAAGA AACCACCAAGGTCCAAAG C GAGCAAGAGAATCCCAGGACAG AAAGGTAAAGCTCCCTCCCTCAAGTTGACAAAAATCTC	993
	GAGATTTTTGTCAACTTGAGGGAGGGAGCTTTACCTTTCTGT CCTGGGATTCTCTTGCTC G CTTTGGACCTTGGTGGTTTCTTC CATTGACCACATCTCCTCTGACTTCAAAATCATGCTG	994
	GTCCAAAG C GAGCAAGA	995
	TCTTGCTC G CTTTGGAC	996
Breast Cancer Gln-1756-Stop CAG to TAG	GTCAGAGGAGATGTGGTCAATGGAAGAAACCACCAAGGTCC AAAGCGAGCAAGAGAATCC C AGGACAGAAAGGTAAAGCTCC CTCCCTCAAGTTGACAAAAATCTCACCCACCACTCTGT	997
	ACAGAGTGGTGGGGTGAGATTTTTGTCAACTTGAGGGAGGG AGCTTTACCTTTCTGTCT G GGATTCTCTTGCTCGCTTTGGA CCTTGGTGGTTTCTTCCATTGACCACATCTCCTCTGAC	998
	GAGAATCC C AGGACAGA	999
	TCTGTCCT G GGATTCTC	1000
Breast Cancer Met-1775-Arg ATG to AGG	CTCTCTTCTTCCAGATCTTCAGGGGGCTAGAAATCTGTTGCT ATGGGCCCTTACCAACATGCCACAGGTAAGAGCCTGGGA GAACCCAGAGTTCCAGCACCAGCCTTTGTCTTACATA	1001
	TATGTAAGACAAAGGCTGGTGTGGAAGTCTGGGGTTCTCCC AGGCTCTTACCTGTGGGC A TGTTGGTGAAGGGCCCATAGCA ACAGATTTCTAGCCCCCTGAAGATCTGGAAGAAGAGAG	1002

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CACCAACATGCCACAG	1003
	CTGTGGGCATGTTGGTG	1004
Breast Cancer Trp-1782-Stop TGG to TGA	AGTATGCAGTACTGCAGTGATTTTACATCTAAATGTCCATT TTAGATCAACTGGAATGGATGGTACAGCTGTGTGGTGCTTCT GTGGTGAAGGAGCTTTCATCATTACCCTTGGCACA	1005
	TGTGCCAAGGGTGAATGATGAAAGCTCCTTCACCACAGAAGC ACCACACAGCTGTACCATCCATTCCAGTTGATCTAAAATGGA CATTTAGATGTAAAATCACTGCAGTAATCTGCATACT	1006
	CTGGAATGGATGGTACA	1007
	TGTACCATCCATTCCAG	1008
Breast Cancer Gln-1785-His CAG to CAT	ATTACTGCAGTGATTTTACATCTAAATGTCCATTTTAGATCAAC TGGAATGGATGGTACAGCTGTGTGGTGCTTCTGTGGTGAAG GAGCTTTCATCATTACCCTTGGCACAGTAAGTATT	1009
	AATACTTACTGTGCCAAGGGTGAATGATGAAAGCTCCTTCAC CACAGAAGCACCACACAGCTGTACCATCCATTCCAGTTGATC TAAAATGGACATTTAGATGTAAAATCACTGCAGTAAT	1010
	ATGGTACAGCTGTGTGG	1011
	CCACACAGCTGTACCAT	1012
Breast Cancer Glu-1794-Asp GAG to GAT	GTCCATTTTAGATCAACTGGAATGGATGGTACAGCTGTGTGG TGCTTCTGTGGTGAAGGAGCTTTCATCATTACCCTTGGCAC AGTAAGTATTGGGTGCCCTGTCAGAGAGGGAGGACAC	1013
	GTGTCCTCCCTCTCTGACAGGGCACCCAATACTTACTGTGCC AAGGGTGAATGATGAAAGCTCCTTCACCACAGAAGCACCACA CAGCTGTACCATCCATTCCAGTTGATCTAAAATGGAC	1014
	GTGAAGGAGCTTTCATC	1015
	GATGAAAGCTCCTTCAC	1016
Breast Cancer Arg-1835-Stop CGA to TGA	CTCTGCTTGTGTTCTCTGTCTCCAGCAATTGGGCAGATGTGT GAGGCACCTGTGGTGACCCGAGAGTGGGTGTTGGACAGTGT AGCACTCTACCAAGTCCAGGAGCTGGACACCTACCTGA	1017
	TCAGGTAGGTGTCCAGCTCCTGGCACTGGTAGAGTGCTACA CTGTCCAACACCCACTCTCGGGTCACCACAGGTGCCTCACA CATCTGCCCAATTGCTGGAGACAGAGAACACAAGCAGAG	1018
	TGGTGACCCGAGAGTGG	1019
	CCACTCTCGGGTCACCA	1020

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Trp-1837-Arg TGG to CGG	TTGTGTTCTCTGTCTCCAGCAATTGGGCAGATGTGTGAGGCA CCTGTGGTGACCCGAGAGTGGGTGTTGGACAGTGTAGCACT CTACCAGTGCCAGGAGCTGGACACCTACCTGATACCCC	1021
	GGGGTATCAGGTAGGTGTCCAGCTCCTGGCACTGGTAGAGT GCTACACTGTCCAACACCCACTCTCGGGTCACCACAGGTGC CTCACACATCTGCCCAATTGCTGGAGACAGAGAACACAA	1022
	CCCGAGAGTGGGTGTTG	1023
	CAACACCCACTCTCGGG	1024
Breast Cancer Trp-1837-Stop TGG to TAG	TGTGTTCTCTGTCTCCAGCAATTGGGCAGATGTGTGAGGCAC CTGTGGTGACCCGAGAGTGGGTGTTGGACAGTGTAGCACTC TACCAGTGCCAGGAGCTGGACACCTACCTGATACCCCA	1025
	TGGGGTATCAGGTAGGTGTCCAGCTCCTGGCACTGGTAGAG TGCTACACTGTCCAACACCCACTCTCGGGTCACCACAGGTG CCTCACACATCTGCCCAATTGCTGGAGACAGAGAACACA	1026
	CCGAGAGTGGGTGTTGG	1027
	CCAACACCCACTCTCGG	1028

Table 15
BRCA2 Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast cancer PHE32LEU TTT to CTT	GTAAACTAAGGTGGGATTTTTTTTTTAAATAGATTTAGGAC CAATAAGTCTTAATTGGTTGAAGAACTTTCTTCAGAAGCTCC ACCCTATAATTCTGAACCTGCAGAAGAATCTGAAC	1029
	GTTGAGATTCTTCTGCAGGTTTCAAGATTATAGGGTGGAGCTT CTGAAGAAAGTTCTTCAACCAATTAAGACTTATTGGTCCTAA ATCTATTTAAAAAAAATCCCACCTTAGTTTTAAC	1030
	TTAATTGGTTTGAAGAA	1031
	TTCTTCAACCAATTA	1032
Breast cancer TYR42CYS TAT to TGT	TAGATTTAGGACCAATAAGTCTTAATTGGTTTGAAGAACTTTC TTCAGAAGCTCCACCCTATAATTCTGAACCTGCAGAAGAATC TGAACATAAAAACAACATTACGAACCAAACCTATT	1033

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AATAGGTTTGGTTCGTAATTGTTGTTTTATGTTTCAGATTCTTC TGCAGGTTTCAGAATTATAGGGTGGAGCTTCTGAAGAAAGTTC TTCAAACCAATTAAGACTTATTGGTCCTAAATCTA	1034
	TCCACCCTATAATTCTG	1035
	CAGAATTATAGGGTGA	1036
Breast cancer LYS53ARG AAA to AGA	AAGAACTTTCTTCAGAAGCTCCACCCTATAATTCTGAACCTGC AGAAGAATCTGAACATAAAAACAACAATTACGAACCAAACCTA TTTAAACTCCACAAAGGAAACCATCTTATAATCA	1037
	TGATTATAAGATGGTTTCCTTTGTGGAGTTTTAAATAGGTTTG GTTTCGTAATTGTTGTTTTATGTTTCAGATTCTTCTGCAGGTTT AGAATTATAGGGTGGAGCTTCTGAAGAAAGTTCTT	1038
	TGAACATAAAAACAACA	1039
	TGTTGTTTTATGTTCA	1040
Breast cancer Phe81Leu TTC to CTC	CTATTTAAACTCCACAAAGGAAACCATCTTATAATCAGCTGG CTTCAACTCCAATAATTTCAAAGAGCAAGGGCTGACTCTGC CGCTGTACCAATCTCCTGTAAAAGAATTAGATAAAT	1041
	ATTTATCTAATTCTTTACAGGAGATTGGTACAGCGGCAGAGT CAGCCCTTGCTCTTTGAATATTATTGGAGTTGAAGCCAGCTG ATTATAAGATGGTTTCCTTTGTGGAGTTTTAAATAG	1042
	CAATAATATTCAAAGAG	1043
	CTCTTTGAATATTATTG	1044
Breast cancer TRP194TERM TGG to TAG	GTCAGACACCAAAACATATTTCTGAAAGTCTAGGAGCTGAGG TGGATCCTGATATGTCTTGTCAAGTTCTTTAGCTACACCACC CACCCTTAGTTCTACTGTGCTCATAGGTAATAATAG	1045
	CTATTATTACCTATGAGCACAGTAGAACTAAGGGTGGGTGGT GTAGCTAAAGAACTTGACCAAGACATATCAGGATCCACCTCA GCTCCTAGACTTTAGAAATATGTTTTGGTGTCTGAC	1046
	TATGTCTTGTCAAGTT	1047
	AACTTGACCAAGACATA	1048
Breast cancer PRO201ARG CCA to CGA	CTGAAAGTCTAGGAGCTGAGGTGGATCCTGATATGTCTTGGT CAAGTTCTTTAGCTACACCACCCACCCTTAGTTCTACTGTGCT CATAGGTAATAATAGCAATGTGTATTTACAAGAAA	1049
	TTTCTTGTAATACACATTTGCTATTATTACCTATGAGCACAGT AGAACTAAGGGTGGGTGGTGTAGCTAAAGAACTTGACCAAGA CATATCAGGATCCACCTCAGCTCCTAGACTTTTCAG	1050

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGCTACAC <u>C</u> ACCCACCC	1051
	GGGTGGGT <u>G</u> GTGTAGCT	1052
Breast cancer Pro222Ser CCT to TCT	ACAATACACATAAATTTTTATCTTACAGTCAGAAATGAAGAAG CATCTGAAACTGTATTT <u>C</u> CTCATGATACTACTGCTGTAAGTAA ATATGACATTGATTAGACTGTTGAAATTGCTAACA	1053
	TGTTAGCAATTTCAACAGTCTAATCAATGTCATATTTACTTACA GCAGTAGTATCATGAGGAAATACAGTTTCAGATGCTTCTTCAT TTCTGACTGTAAGATAAAAATTTATGTGTATTGT	1054
	CTGTATTT <u>C</u> CTCATGAT	1055
	ATCATGAGGAAATACAG	1056
Breast cancer Leu-414-Term TTG to TAG	AATGGTCTCAACTAACCCCTTTCAGGTCTAAATGGAGCCCAGA TGGAGAAAATACCCCTATTGCATATTTCTTCATGTACCAAAA TATTTGAGAAAAGACCTATTAGACACAGAGAACAA	1057
	TTGTTCTCTGTGTCTAATAGGTCTTTTCTGAAATATTTTGGTC ACATGAAGAAATATGCAATAGGGGTATTTTCTCCATCTGGGC TCCATTTAGACCTGAAAGGGTTAGTTGAGACCATT	1058
	ACCCCTATTGCATATTT	1059
	AAATATGCAATAGGGGT	1060
Breast cancer, male Cys554Trp TGT to TGG	AGCCTCTGAAAGTGGACTGGAAATACATACTGTTTGCTCACA GAAGGAGGACTCCTTATGTCCAAATTTAATTGATAATGGAAG CTGGCCAGCCACCACCACACAGAATTCTGTAGCTTTG	1061
	CAAAGCTACAGAATTCTGTGTGGTGGTGGCTGGCCAGCTTC CATTATCAATTAATTTGGACATAAGGAGTCCTCCTTCTGTGA GCAAACAGTATGTATTTCCAGTCCACTTTCAGAGGCT	1062
	TCCTTATGTCCAAATTT	1063
	AAATTTGGACATAAGGA	1064
Breast cancer Lys944Term AAA to TAA	AACTCTACCATGGTTTTATATGGAGACACAGGTGATAAACAA GCAACCCAAGTGTCAATTAAAAAGATTGGTTTATGTTCTTG CAGAGGAGAACAAAAATAGTGTAAGCAGCATATAA	1065
	TTATATGCTGCTTTACACTATTTTTGTTCTCCTCTGCAAGAAC ATAAACCAATCTTTTTTAATTGACACTTGGGTTGCTTGTAT CACCTGTGTCTCCATATAAACCATGGTAGAGTT	1066
	TGTCAATTAAAAAGAT	1067
	ATCTTTTTTAATTGACA	1068

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast cancer, male Glu1320Term GAA to TAA	ATGACTACTGGCACTTTTGTGAAGAAATTACTGAAAATTACA AGAGAAATACTGAAAATGAAGATAACAAATATACTGCTGCCAG TAGAAATTCTCATAACTTAGAATTTGATGGCAGTG	1069
	CACTGCCATCAAATTCTAAGTTATGAGAATTTCTACTGGCAGC AGTATATTTGTTATCTTCATTTTCAGTATTTCTCTTGTAAATTTTC AGTAATTTCTTCAACAAAAGTGCCAGTAGTCAT	1070
	CTGAAAATGAAGATAAC	1071
	GTTATCTTCATTTTCAG	1072
Breast cancer Glu1876Term GAA to TAA	CATGAAACAATTAAAAAAGTGAAAGACATATTTACAGACAGTT TCAGTAAAGTAATTAAGGAAAACAACGAGAATAAATCAAAAAT TTGCCAAACGAAAATTATGGCAGGTTGTTACGAGG	1073
	CCTCGTAACAACCTGCCATAATTTTCGTTTGGCAAATTTTGA TTTATTCTCGTTGTTTTCTTAATTACTTTACTGAAACTGTCTG TAAATATGTCTTCACTTTTTTAATTGTTTCATG	1074
	TAATTAAGGAAAACAAC	1075
	GTTGTTTTCTTAATTA	1076
Breast cancer Ser1882Term TCA to TAA	TGAAAGACATATTTACAGACAGTTTCAGTAAAGTAATTAAGGA AAACAACGAGAATAAATCAAAAATTTGCCAAACGAAAATTATG GCAGGTTGTTACGAGGCATTGGATGATTCAGAGGA	1077
	TCCTCTGAATCATCCAATGCCTCGTAACAACCTGCCATAATTT TCGTTTGGCAAATTTTGATTTATTCTCGTTGTTTTCTTAATT ACTTACTGAAACTGTCTGTAAATATGTCTTCA	1078
	GAATAATCAAAAATTT	1079
	AAATTTTTGATTTATTC	1080
Breast cancer Glu1953Term GAA to TAA	AACCAAAATATGTCTGGATTGGAGAAAGTTTCTAAAATATCAC CTTGATGTTAGTTTGGAAACTTCAGATATATGTAAATGTAG TATAGGGAAGCTTCATAAGTCAGTCTCATCTGCAA	1081
	TTGCAGATGAGACTGACTTATGAAGCTTCCCTATACTACATTT ACATATATCTGAAGTTTCAAACCTAACATCACAAGGTGATATT TTAGAACTTTCTCCAATCCAGACATATTTGGTT	1082
	TTAGTTTGGAAACTTCA	1083
	TGAAGTTTCAAACCTAA	1084
Breast cancer Ser1970Term TCA to TAA	TTAGTTTGGAAACTTCAGATATATGTAAATGTAGTATAGGGAA GCTTCATAAGTCAGTCTCATCTGCAAATACTTGTGGGATTTT AGCACAGCAAGTGAAAATCTGTCCAGGTATCAGA	1085

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TCTGATACCTGGACAGATTTTCCACTTGCTGTGCTAAAAATCC CACAAGTATTTGCAGATGAGACTGACTTATGAAGCTTCCCTAT ACTACATTTACATATATCTGAAGTTTCCAACTAA	1086
	GTCAGTCTCATCTGCAA	1087
	TTGCAGATGAGACTGAC	1088
Breast cancer Gln1987Term CAG to TAG	AAGTCAGTCTCATCTGCAAATACTTGTGGGATTTTATGCACAG CAAGTGGAAAATCTGTCCAGGTATCAGATGCTTCATTACAAAA CGCAAGACAAGTGTTTTCTGAAATAGAAGATAGTA	1089
	TACTATCTTCTATTTTCAGAAAACACTTGTCTTGCGTTTTGTAAT GAAGCATCTGATACCTGGACAGATTTTCCACTTGCTGTGCTA AAAATCCCACAAGTATTTGCAGATGAGACTGACTT	1090
	AATCTGTCCAGGTATCA	1091
	TGATACCTGGACAGATT	1092
Breast cancer Ala246Val GCA to GTA	AAAATAAGATTAATGACAATGAGATTCATCAGTTTAACAAAA CAACTCCAATCAAGCAGCAGCTGTAACCTTTCACAAAGTGTGA AGAAGAACCTTTAGGTATTGTATGACAATTTGTGTG	1093
	CACACAAATTGTCATACAATACCTAAAGGTTCTTCTTCACACT TTGTGAAAGTTACAGCTGCTGCTTGATTGGAGTTGTTTTGTT AAACTGATGAATCTCATTGTCATTAATCTTATTTT	1094
	TCAAGCAGCAGCTGTAA	1095
	TTACAGCTGCTGCTTGA	1096
Breast cancer Arg2520Term CGA to TGA	AGGCAACGCGTCTTTCCACAGCCAGGCAGTCTGTATCTTGCA AAAACATCCACTCTGCCTCGAATCTCTCTGAAAGCAGCAGTA GGAGGCCAAGTCCCCTCTGCGTGTCTCATAAACAGG	1097
	CCTGTTTATGAGGACACGCAGAGGGGACTTGGCCTCCTACT GCTGCTTTCAGAGAGATTCCAGGCAGAGTGGATGTTTTGCA AGATACAGACTGCCTGGCTGTGGAAAGACGCGTTGCCT	1098
	CTCTGCCTCGAATCTCT	1099
	AGAGATTCCAGGCAGAG	1100
Breast cancer Gln2714Term CAA to TAA	ATTCATTGAGCGCAAATATATCTGAAACTTCTAGCAATAAAA CTAGTAGTGAGATACCCAAAAAGTGGCCATTATTGAACCTTA CAGATGGGTGGTATGCTGTAAAGGCCAGTTAGATC	1101
	GATCTAACTGGGCCTTAACAGCATACCACCCATCTGTAAGTT CAATAATGGCCACTTTTTGGGTATCTGCACTACTAGTTTTATT GCTAGAAGTTTCAGATATATTTGCGCTCAATGAAAT	1102

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CAGATACCC <u>C</u> AAAAAGTG	1103
	CACTTTTTG <u>G</u> GTATCTG	1104
Breast cancer Leu2776Term TTA to TGA	CAGAACTGGTGGGCTCTCCTGATGCCTGTACACCTCTTGAAG CCCCAGAATCTCTTATGTTAAAGGTAAATTAATTTGCACTCTT GGTAAAAATCAGTCATTGATTAGTTAAATTCTAGA	1105
	TCTAGAATTTAACTGAATCAATGACTGATTTTTACCAAGAGTG CAAATTAATTTACCTTTAACATAAGAGATTCTGGGGCTTCAAG AGGTGTACAGGCATCAGGAGAGCCCACCAGTTCTG	1106
	TCTTATGT <u>T</u> AAAGATTT	1107
	AAATCTTTA <u>A</u> CATAAGA	1108
Breast cancer Gln2893Term CAG to TAG	CCTTTTGTTTTCTTAGAAAAACACAACAAAACCATATTTACCATC ACGTGCACTAACAAGACAGCAAGTTCGTGCTTTGCAAGATGG TGCAGAGCTTTATGAAGCAGTGAAGAATGCAGCAG	1109
	CTGCTGCATTCTTCACTGCTTCATAAAGCTCTGCACCATCTTG CAAAGCACGAACCTTGCTGTCTTGTTAGTGCACGTGATGGTAA ATATGGTTTTGTTGTGTTTTCTAAGAAAACAAAAGG	1110
	TAACAAGACAGCAAGTT	1111
	AACTTGCTGTCTTGTTA	1112
Breast cancer Ala2951Thr GCC to ACC	AATCACAGGCAAATGTTGAATGATAAGAAACAAGCTCAGATC CAGTTGGAAATTAGGAAGGCCATGGAATCTGCTGAACAAAAG GAACAAGGTTTATCAAGGGATGTCACAACCGTGTGGA	1113
	TCCACACGGTTGTGACATCCCTTGATAAACCTTGTTCCCTTTTG TTCAGCAGATTCCATGGCCTTCCTAATTTCCAACCTGGATCTGA GCTTGTTTCTTATCATTCAACATTTGCCTGTGATT	1114
	TTAGGAAGGCCATGGAA	1115
	TTCCATGGCCTTCCTAA	1116
Breast cancer Met3118Thr ATG to ACG	ACAATTTACTGGCAATAAAGTTTTGGATAGACCTTAATGAGGA CATTATTAAGCCTCATATGTTAATTGCTGCAAGCAACCTCCAG TGCGCACCAGAATCCAAATCAGGCCTTCTTACTTT	1117
	AAAGTAAGAAGGCCTGATTTGGATTCTGGTCGCCACTGGAG GTTGCTTGCAGCAATTAACATATGAGGCTTAATAATGTCCTCA TTAAGGTCTATCCAAAACCTTTATTGCCAGTAAATTGT	1118
	GCCTCATATGTTAATTG	1119
	CAATTAACATATGAGGC	1120

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast cancer Thr3401Met ACG to ATG	GACTGAAACGACGTTGTACTACATCTCTGATCAAAGAACAGG AGAGTTCCCAGGCCAGTACGGAAGAATGTGAGAAAAATAAGC AGGACACAATTACAATAAAAAATATATCTAAGCATT	1121
	AATGCTTAGATATATTTTTAGTTGTAATTGTGTCCTGCTTATT TTTCTCACATTCTTCCGTAAGTGGCCTGGGAAGTCTCCTGTTCT TTGATCAGAGATGTAGTACAACGTCGTTTCAGTC	1122
	GGCCAGTACGGAAGAAT	1123
	ATTCTTCCGTAAGTGGCC	1124
Breast cancer Ile3412Val ATT to GTT	AAAGAACAGGAGAGTTCCCAGGCCAGTACGGAAGAATGTGA GAAAAATAAGCAGGACACAATTACAATAAAAAATATATCTAA GCATTTGCAAAGGCGACAATAAATTATTGACGCTTAA	1125
	TTAAGCGTCAATAATTTATTGTGCGCTTTGCAAATGCTTAGAT ATATTTTTAGTTGTAATTGTGTCCTGCTTATTTTCTCACATT CTTCCGTAAGTGGCCTGGGAAGTCTCCTGTTCTTT	1126
	AGGACACAATTACAATA	1127
	AGTTGTAATTGTGTCCT	1128

EXAMPLE 9 Cystic Fibrosis - CFTR

Cystic fibrosis is a lethal disease affecting approximately one in 2,500 live Caucasian births and is the most common autosomal recessive disease in Caucasians. Patients with this disease have reduced chloride ion permeability in the secretory and absorptive cells of organs with epithelial cell linings, including the airways, pancreas, intestine, sweat glands and male genital tract. This, in turn, reduces the transport of water across the epithelia. The lungs and the GI tract are the predominant organ systems affected in this disease and the pathology is characterized by blocking of the respiratory and GI tracts with viscous mucus. The chloride impermeability in affected tissues is due to mutations in a specific chloride channel, the cystic fibrosis transmembrane conductance regulator protein (CFTR), which prevents normal passage of chloride ions through the cell membrane (Welsh et al., Neuron, 8:821-829 (1992)). Damage to the lungs due to mucus blockage, frequent bacterial infections and inflammation is the primary cause of morbidity and mortality in CF patients and, although maintenance therapy has improved the quality of patients' lives, the median age at death is still only around 30 years. There is no effective treatment for the disease, and therapeutic research is focused on gene therapy using

exogenous transgenes in viral vectors and/or activating the defective or other chloride channels in the cell membrane to normalize chloride permeability (Tizzano et al., J. Pediat., 120:337-349 (1992)). However, the death of a teenage patient treated with an adenovirus vector carrying an exogenous CFTR gene in clinical trials in the late 1990's has impacted this area of research.

5 The oligonucleotides of the invention for correction of the CFTR gene are attached as a table.

Table 16
CFTR Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Ala46Asp GCT to GAT	AAGGATACAGACAGCGCCTGGAATTGTCAGACATATACCAA TCCCTTCTGTTGATTCTGCTGACAATCTATCTGAAAAATTGGA AAGGTATGTTTCATGTACATTGTTAGTTGAAGAGAG	1129
	CTCTCTTCAACTAAACAATGTACATGAACATACCTTTCCAATTT TTCAGATAGATTGTCAGCAGAATCAACAGAAGGGATTGGTA TATGTCTGACAATTCCAGGCGCTGTCTGTATCCTT	1130
	TGATTCTGCTGACAATC	1131
	GATTGTCAGCAGAATCA	1132
Cystic fibrosis Ser50Tyr TCT to TAT	AGCGCCTGGAATTGTCAGACATATACCAAATCCCTTCTGTTG ATTCTGCTGACAATCTATCTGAAAAATTGGAAAGGTATGTTCA TGACATTGTTTAGTTGAAGAGAGAAATTCATATTA	1133
	TAATATGAATTTCTCTCTTCAACTAAACAATGTACATGAACATA CCTTTCCAATTTTTCAGATAGATTGTCAGCAGAATCAACAGAA GGGATTGGTATATGTCTGACAATTCCAGGCGCT	1134
	CAATCTATCTGAAAAAT	1135
	ATTTTTCAGATAGATTG	1136
Congenital absence of vas deferens Glu56Lys GAA-AAA	AGGACAACATAAAATATTTGCACATGCAACTTATTGGTCCCACT TTTTATTCTTTTGCAGAGAAATGGGATAGAGAGCTGGCTTCAA GAAAAATCCTAACTCATTAAATGCCCTTCGGCGAT	1137
	ATCGCCGAAGGGCATTAAATGAGTTTAGGATTTTCTTTGAAGC CAGCTCTCTATCCATTCTCTGCAAAAGAATAAAAAGTGGGA CCAATAAGTTGCATGTGCAAATATTTAGTTGTCCT	1138
	TITGCAGAGAAATGGGAT	1139
	ATCCCATTTCTCTGCAAA	1140

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Trp57Gly TGG to GGG	AGGACAACCTAAAATATTTGCACATGCAACTTATTGGTCCCCT TTTTATTCTTTTGCAGAGAAATGGGATAGAGAGCTGGCTTCAAA GAAAAATCCTAAACTCATTAAATGCCCTTCGGCGAT	1141
	ATCGCCGAAGGGCATTAAATGAGTTTAGGATTTTCTTTGAAGC CAGCTCTCTATCCCATTCTCTGCAAAAGAATAAAAAAGTGGGA CCAATAAGTTGCATGTGCAATATTTTAGTTGTCCT	1142
	TTTGCAGAGAAATGGGAT	1143
	ATCCCATTCTCTGCAAA	1144
Cystic fibrosis Trp57Term TGG to TGA	AACTAAAATATTTGCACATGCAACTTATTGGTCCCCTTTTAT TCTTTTGCAGAGAATGGGATAGAGAGCTGGCTTCAAAGAAAA ATCCTAAACTCATTAAATGCCCTTCGGCGATGTTTT	1145
	AAAACATCGCCGAAGGGCATTAAATGAGTTTAGGATTTTCTTT GAAGCCAGCTCTCTATCCCATTCTCTGCAAAAGAATAAAAAAGT GGGACCAATAAGTTGCATGTGCAATATTTTAGTT	1146
	AGAGAATGGGATAGAGA	1147
	TCTCTATCCCATTCTCT	1148
Congenital absence of vas deferens Asp58Asn GAT to AAT	ACTAAAATATTTGCACATGCAACTTATTGGTCCCCTTTTATT CTTTTGCAGAGAATGGGATAGAGAGCTGGCTTCAAAGAAAA TCCTAAACTCATTAAATGCCCTTCGGCGATGTTTT	1149
	AAAAACATCGCCGAAGGGCATTAAATGAGTTTAGGATTTTCTT TGAAGCCAGCTCTCTATCCCATTCTCTGCAAAAGAATAAAAAAG TGGGACCAATAAGTTGCATGTGCAATATTTTAGT	1150
	GAGAATGGGATAGAGAG	1151
	CTCTCTATCCCATTCTC	1152
Cystic fibrosis Glu60Term GAG to TAG	ATATTTGCACATGCAACTTATTGGTCCCCTTTTATTCTTTT CAGAGAATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCTAA ACTCATTAAATGCCCTTCGGCGATGTTTTTCTGGA	1153
	TCCAGAAAAAACATCGCCGAAGGGCATTAAATGAGTTTAGGAT TTTTCTTTGAAGCCAGCTCTCTATCCCATTCTCTGCAAAAGAA TAAAAAGTGGGACCAATAAGTTGCATGTGCAATAT	1154
	GGGATAGAGAGCTGGCT	1155
	AGCCAGCTCTCTATCCC	1156

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Pro67Leu CCT to CTT	GGTCCCACTTTTTATTCTTTTGCAGAGAATGGGATAGAGAGC TGGCTTCAAAGAAAAATCCTAACTCATTAAATGCCCTTCGGC GATGTTTTCTGGAGATTATGTTCTATGGAATCTT	1157
	AAGATTCCATAGAACATAAATCTCCAGAAAAACATCGCCGAA GGGCATTAATGAGTTTAGGATTTTTCTTTGAAGCCAGCTCTCT ATCCATTCTCTGCAAAAGAATAAAAAGTGGGACC	1158
	GAAAAATCCTAACTCA	1159
	TGAGTTTAGGATTTTTCT	1160
Cystic fibrosis Arg74Trp CGG to TGG	TGCAGAGAATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCT AACTCATTAAATGCCCTTCGGCGATGTTTTCTGGAGATTTA TGTTCTATGGAATCTTTTTATATTAGGGTAAGGA	1161
	TCCTTACCCCTAAATATAAAAAGATTCCATAGAACATAAATCT CCAGAAAAACATCGCCGAAGGGCATTAAATGAGTTTAGGATT TTTCTTTGAAGCCAGCTCTCTATCCATTCTCTGCA	1162
	ATGCCCTTCGGCGATGT	1163
	ACATCGCCGAAGGGCAT	1164
Congenital absence of vas deferens ARG75GLN CGA to CAA	GAGAATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCTAAAC TCATTAATGCCCTTCGGCGATGTTTTCTGGAGATTTATGTT CTATGGAATCTTTTTATATTAGGGTAAGGATCTC	1165
	GAGATCCTTACCCCTAAATATAAAAAGATTCCATAGAACATAA ATCTCCAGAAAAACATCGCCGAAGGGCATTAAATGAGTTTAG GATTTTTCTTTGAAGCCAGCTCTCTATCCATTCTC	1166
	CCTTCGGCGATGTTTTT	1167
	AAAAACATCGCCGAAGG	1168
Cystic fibrosis Arg75Leu CGA to CTA	GAGAATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCTAAAC TCATTAATGCCCTTCGGCGATGTTTTCTGGAGATTTATGTT CTATGGAATCTTTTTATATTAGGGTAAGGATCTC	1169
	GAGATCCTTACCCCTAAATATAAAAAGATTCCATAGAACATAA ATCTCCAGAAAAACATCGCCGAAGGGCATTAAATGAGTTTAG GATTTTTCTTTGAAGCCAGCTCTCTATCCATTCTC	1170
	CCTTCGGCGATGTTTTT	1171
	AAAAACATCGCCGAAGG	1172
Cystic fibrosis Arg75Term CGA to TGA	AGAGAATGGGATAGAGAGCTGGCTTCAAAGAAAAATCCTAAA CTCATTAAATGCCCTTCGGCGATGTTTTCTGGAGATTTATGT TCTATGGAATCTTTTTATATTAGGGTAAGGATCT	1173

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGATCCTTACCCCTAAATATAAAAAAGATTCCATAGAACATAAA TCTCCAGAAAAACATCGCCGAAGGGCATTAAATGAGTTTAGG ATTTTCTTTGAAGCCAGCTCTCTATCCCATTCTCT	1174
	CCCTTCGGCGATGTTTT	1175
	AAAACATCGCCGAAGGG	1176
Cystic fibrosis Gly85Glu GGA to GAA	AAAATCCTAAACTCATTAAATGCCCTTCGGCGATGTTTTTCTG GAGATTTATGTTCTATGGAATCTTTTATATTTAGGGGTAAGG ATCTCATTTGTACATTCATTATGTATCACATAACT	1177
	AGTTATGTGATACATAATGAATGTACAAATGAGATCCTTACCC CTAAATATAAAAAAGATTCCATAGAACATAAATCTCCAGAAAA ACATCGCCGAAGGGCATTAAATGAGTTTAGGATTTT	1178
	GTTCTATGGAATCTTTT	1179
	AAAAGATTCCATAGAAC	1180
Cystic fibrosis Gly85Val GGA to GTA	AAAATCCTAAACTCATTAAATGCCCTTCGGCGATGTTTTTCTG GAGATTTATGTTCTATGGAATCTTTTATATTTAGGGGTAAGG ATCTCATTTGTACATTCATTATGTATCACATAACT	1181
	AGTTATGTGATACATAATGAATGTACAAATGAGATCCTTACCC CTAAATATAAAAAAGATTCCATAGAACATAAATCTCCAGAAAA ACATCGCCGAAGGGCATTAAATGAGTTTAGGATTTT	1182
	GTTCTATGGAATCTTTT	1183
	AAAAGATTCCATAGAAC	1184
Cystic fibrosis Leu88Ser TTA to TCA	AACTCATTAAATGCCCTTCGGCGATGTTTTTCTGGAGATTTAT GTTCTATGGAATCTTTTATATTTAGGGGTAAGGATCTCATTT GTACATTCATTATGTATCACATAACTATATGCATT	1185
	AATGCATATAGTTATGTGATACATAATGAATGTACAAATGAGA TCCTTACCCCTAAATATAAAAAAGATTCCATAGAACATAAATCT CCAGAAAAACATCGCCGAAGGGCATTAAATGAGTT	1186
	AATCTTTTATATTTAG	1187
	CTAAATATAAAAAAGATT	1188
Cystic fibrosis Phe87Leu TTT to CTT	CCTAAACTCATTAAATGCCCTTCGGCGATGTTTTTCTGGAGAT TTATGTTCTATGGAATCTTTTATATTTAGGGGTAAGGATCTC ATTTGTACATTCATTATGTATCACATAACTATATG	1189
	CATATAGTTATGTGATACATAATGAATGTACAAATGAGATCCT TACCCCTAAATATAAAAAAGATTCCATAGAACATAAATCTCCAG AAAAACATCGCCGAAGGGCATTAAATGAGTTTAGG	1190

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGGAATC <u>I</u> TTTTATAT	1191
	ATATAAAA <u>A</u> GATTCCAT	1192
Cystic fibrosis Leu88Term TTA to TGA	AACTCATTAAATGCCCTTCGGCGATGTTTTCTGGAGATTTAT GTTCTATGGAATCTTTT <u>I</u> ATATTTAGGGGTAAGGATCTCATT GTACATTCATTATGTATCACATAACTATATGCATT	1193
	AATGCATATAGTTATGTGATACATAATGAATGTACAAATGAGA TCCTTACCCCTAAATATA <u>AAAA</u> AGATTCCATAGAACATAAATCT CCAGAAAAAACATCGCCGAAGGGCATTAAATGAGTT	1194
	AATCTTTT <u>I</u> ATATTTAG	1195
	CTAAATATA <u>AAAA</u> AGATT	1196
Cystic fibrosis Leu88Term TTA to TAA	AACTCATTAAATGCCCTTCGGCGATGTTTTCTGGAGATTTAT GTTCTATGGAATCTTTT <u>I</u> ATATTTAGGGGTAAGGATCTCATT GTACATTCATTATGTATCACATAACTATATGCATT	1197
	AATGCATATAGTTATGTGATACATAATGAATGTACAAATGAGA TCCTTACCCCTAAATATA <u>AAAA</u> AGATTCCATAGAACATAAATCT CCAGAAAAAACATCGCCGAAGGGCATTAAATGAGTT	1198
	AATCTTTT <u>I</u> ATATTTAG	1199
	CTAAATATA <u>AAAA</u> AGATT	1200
Cystic fibrosis Gly91Arg GGG to AGG	AATGCCCTTCGGCGATGTTTTCTGGAGATTTATGTTCTATG GAATCTTTTATATTTA <u>G</u> GGGTAAGGATCTCATTGTACATTC ATTATGTATCACATAACTATATGCATTTTGTGAT	1201
	ATCACAAAATGCATATAGTTATGTGATACATAATGAATGTAC AAATGAGATCCTTACCC <u>C</u> TAAATATAAAAAAGATTCCATAGAAC ATAAATCTCCAGAAAAAACATCGCCGAAGGGCATT	1202
	TATATTTA <u>G</u> GGGTAAGG	1203
	CCTTACCC <u>C</u> TAAATATA	1204
Cystic fibrosis Gln98Arg CAG to CGG	AATAAATGAAATTTAATTTCTCTGTTTTCCCTTTTGTAGGAA GTCACCAAAGCAGTACA <u>G</u> CCTCTCTTACTGGGAAGAATCATA GCTTCCTATGACCCGGATAACAAGGAGGAACGCTC	1205
	GAGCGTTCCTCCTTGTTATCCGGGTCATAGGAAGCTATGATT CTTCCCAGTAAGAGAGGCT <u>G</u> TACTGCTTTGGTGACTTCCTAC AAAAGGGGAAAAACAGAGAAATTAATTTCAATTTATT	1206
	AGCAGTACA <u>G</u> CCTCTCT	1207
	AGAGAGGCT <u>G</u> TACTGCT	1208

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Gln98Term CAG-TAG	AAATAAATGAAATTTAATTTCTCTGTTTTCCCTTTTGTAGGA AGTCACCAAAGCAGTACAGCCTCTCTTACTGGGAAGAATCAT AGCTTCCTATGACCCGGATAACAAGGAGGAACGCT	1209
	AGCGTTCCTCCTTGTTATCCGGGTCATAGGAAGCTATGATTC TTCCCAGTAAGAGAGGCTGTACTGCTTTGGTGACTTCCTACA AAAGGGGAAAAACAGAGAAATTAATTTTCATTTATTT	1210
	AAGCAGTACAGCCTCTC	1211
	GAGAGGCTGTACTGCTT	1212
Cystic fibrosis Ser108Phe TCC to TTC	CCCTTTTGTAGGAAGTCACCAAAGCAGTACAGCCTCTCTTAC TGGGAAGAATCATAGCTTCTCTATGACCCGGATAACAAGGAGG AACGCTCTATCGCGATTTATCTAGGCATAGGCTTATG	1213
	CATAAGCCTATGCCTAGATAAATCGCGATAGAGCGTTCCTCC TTGTTATCCGGGTCATAGGAAGCTATGATTCTTCCCAGTAAG AGAGGCTGTACTGCTTTGGTGACTTCCTACAAAAGGG	1214
	CATAGCTTCTCTATGACC	1215
	GGTCATAGGAAGCTATG	1216
Cystic fibrosis Tyr109Cys TAT to TGT	TTTTGTAGGAAGTCACCAAAGCAGTACAGCCTCTCTTACTGG GAAGAATCATAGCTTCTCTATGACCCGGATAACAAGGAGGAAC GCTCTATCGCGATTTATCTAGGCATAGGCTTATGCCT	1217
	AGGCATAAGCCTATGCCTAGATAAATCGCGATAGAGCGTTCCT TCCTTGTTATCCGGGTCATAGGAAGCTATGATTCTTCCCAGT AAGAGAGGCTGTACTGCTTTGGTGACTTCCTACAAAA	1218
	AGCTTCCTATGACCCGG	1219
	CCGGGTCAIAGGAAGCT	1220
Cystic fibrosis Asp110His GAC to CAC	TTGTAGGAAGTCACCAAAGCAGTACAGCCTCTCTTACTGGGA AGAATCATAGCTTCTCTATGACCCGGATAACAAGGAGGAACGC TCTATCGCGATTTATCTAGGCATAGGCTTATGCCTTC	1221
	GAAGGCATAAGCCTATGCCTAGATAAATCGCGATAGAGCGTT CCTCCTTGTTATCCGGGTCTATAGGAAGCTATGATTCTTCCCA GTAAGAGAGGCTGTACTGCTTTGGTGACTTCCTACAA	1222
	CTTCCTATGACCCGGAT	1223
	ATCCGGGTCTATAGGAAG	1224

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Congenital absence of vas deferens Pro111Leu CCG to CTG	AGGAAGTCACCAAAGCAGTACAGCCTCTCTTACTGGGAAGAA TCATAGCTTCCTATGACCCGGATAACAAGGAGGAACGCTCTA TCGCGATTTATCTAGGCATAGGCTTATGCCTTCTCTT	1225
	AAGAGAAGGCATAAGCCTATGCCTAGATAAATCGCGATAGAG CGTTCCTCCTTGTTATCCGGGTCATAGGAAGCTATGATTCTT CCCAGTAAGAGAGGCTGTACTGCTTTGGTGACTTCCT	1226
	CTATGACCCGGATAACA	1227
	TGTTATCCGGGTCATAG	1228
Cystic fibrosis Arg117Cys CGC to TGC	GTACAGCCTCTCTTACTGGGAAGAATCATAGCTTCCTATGAC CCGGATAACAAGGAGGAACGCTCTATCGCGATTTATCTAGGC ATAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGC	1229
	GCAGTGTCTCACAATAAAGAGAAGGCATAAGCCTATGCCTA GATAAATCGCGATAGAGCGTTCCTCCTTGTTATCCGGGTCA AGGAAGCTATGATTCTTCCCAGTAAGAGAGGCTGTAC	1230
	AGGAGGAACGCTCTATC	1231
	GATAGAGCGTTCCTCCT	1232
Cystic fibrosis Arg117His CGC to CAC	TACAGCCTCTCTTACTGGGAAGAATCATAGCTTCCTATGACC CGGATAACAAGGAGGAACGCTCTATCGCGATTTATCTAGGCA TAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGCT	1233
	AGCAGTGTCTCACAATAAAGAGAAGGCATAAGCCTATGCCT AGATAAATCGCGATAGAGCGTTCCTCCTTGTTATCCGGGTCA TAGGAAGCTATGATTCTTCCCAGTAAGAGAGGCTGTA	1234
	GGAGGAACGCTCTATCG	1235
	CGATAGAGCGTTCCTCC	1236
Cystic fibrosis Arg117Leu CGC to CTC	TACAGCCTCTCTTACTGGGAAGAATCATAGCTTCCTATGACC CGGATAACAAGGAGGAACGCTCTATCGCGATTTATCTAGGCA TAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGCT	1237
	AGCAGTGTCTCACAATAAAGAGAAGGCATAAGCCTATGCCT AGATAAATCGCGATAGAGCGTTCCTCCTTGTTATCCGGGTCA TAGGAAGCTATGATTCTTCCCAGTAAGAGAGGCTGTA	1238
	GGAGGAACGCTCTATCG	1239
	CGATAGAGCGTTCCTCC	1240

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Arg117Pro CGC to CCC	TACAGCCTCTCTTACTGGGAAGAATCATAGCTTCCTATGACC CGGATAACAAGGAGGAACGCTCTATCGCGATTTATCTAGGCA TAGGCTTATGCCTTCTCTTTATTGTGAGGACACTGCT	1241
	AGCAGTGTCTCACAATAAAGAGAAGGCATAAGCCTATGCCT AGATAAATCGCGATAGAGCGTTCCTCCTTGTATCCGGGTCA TAGGAAGCTATGATTCTTCCCAGTAAGAGAGGCTGTA	1242
	GGAGGAACGCTCTATCG	1243
	CGATAGAGCGTTCCTCC	1244
Cystic fibrosis Ala120Thr GCG-ACG	CTCTTACTGGGAAGAATCATAGCTTCCTATGACCCGGATAAC AAGGAGGAACGCTCTATCGCGATTTATCTAGGCATAGGCTTA TGCCTTCTCTTTATTGTGAGGACACTGCTCCTACACC	1245
	GGTGTAGGAGCAGTGTCTCACAATAAAGAGAAGGCATAAG CCTATGCCTAGATAAATCGCGATAGAGCGTTCCTCCTTGTTA TCCGGGTCATAGGAAGCTATGATTCTTCCCAGTAAGAG	1246
	GCTCTATCGCGATTTAT	1247
	ATAAATCGCGATAGAGC	1248
Cystic fibrosis Tyr122Term TAT to TAA	GGGAAGAATCATAGCTTCCTATGACCCGGATAACAAGGAGGA ACGCTCTATCGCGATTTATCTAGGCATAGGCTTATGCCTTCT CTTTATTGTGAGGACACTGCTCCTACACCCAGCCATT	1249
	AATGGCTGGGTGTAGGAGCAGTGTCTCACAATAAAGAGAA GGCATAAGCCTATGCCTAGATAAATCGCGATAGAGCGTTCCT CCTTGTTATCCGGGTCATAGGAAGCTATGATTCTTCCC	1250
	GCGATTTATCTAGGCAT	1251
	ATGCCTAGATAAATCGC	1252
Cystic fibrosis Gly126Asp GGC-GAC	TAGCTTCCTATGACCCGGATAACAAGGAGGAACGCTCTATCG CGATTTATCTAGGCATAGGCTTATGCCTTCTCTTTATTGTGAG GACACTGCTCCTACACCCAGCCATTTTGGCCTTCA	1253
	TGAAGGCCAAAAATGGCTGGGTGTAGGAGCAGTGTCTCAC AATAAAGAGAAGGCATAAGCCTATGCCTAGATAAATCGCGAT AGAGCGTTCCTCCTTGTATCCGGGTCATAGGAAGCTA	1254
	AGGCATAGGCTTATGCC	1255
	GGCATAAGCCTATGCCT	1256

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis His139Arg CAC to CGC	TCGCGATTTATCTAGGCATAGGCTTATGCCTTCTCTTTATTGT GAGGACACTGCTCCTAC <u>ACCCAGCC</u> ATTTTTGGCCTTCATCA CATTGGAATGCAGATGAGAATAGCTATGTTTAGTTT	1257
	AAACTAAACATAGCTATTCTCATCTGCATTCCAATGTGATGAA GGCCAAAAATGGCTGGG <u>T</u> GTAGGAGCAGTGTCTCACAATA AAGAGAAGGCATAAGCCTATGCCTAGATAAATCGCGA	1258
	GCTCCTAC <u>ACCCAGCC</u> A	1259
	TGGCTGGG <u>T</u> GTAGGAGC	1260
Cystic fibrosis Ala141Asp GCC to GAC	TTTATCTAGGCATAGGCTTATGCCTTCTCTTTATTGTGAGGAC ACTGCTCCTACACCCAG <u>C</u> CATTTTTGGCCTTCATCACATTGG AATGCAGATGAGAATAGCTATGTTTAGTTTGATTGA	1261
	TAAATCAAACAACTAAACATAGCTATTCTCATCTGCATTCCAATGT GATGAAGGCCAAAAATGG <u>C</u> TGGGTGTAGGAGCAGTGTCTC ACAATAAAGAGAAGGCATAAGCCTATGCCTAGATAAA	1262
	ACACCCAG <u>C</u> CATTTTTG	1263
	CAAAAATGG <u>C</u> TGGGTGT	1264
Cystic fibrosis Ile148Thr ATT to ACT	GCCTTCTCTTTATTGTGAGGACACTGCTCCTACACCCAGCCA TTTTTGGCCTTCATCACAT <u>T</u> GGAATGCAGATGAGAATAGCTAT GTTTAGTTTGATTATAAGAAGGTAATACTTCCTTG	1265
	CAAGGAAGTATTACCTTCTTATAAATCAAACAACTAAACATAGCTA TTCTCATCTGCATTCCA <u>A</u> TGTGATGAAGGCCAAAAATGGCTG GGTGTAGGAGCAGTGTCTCACAATAAAGAGAAGGC	1266
	TCATCACAT <u>T</u> GGAATGC	1267
	GCATTCCA <u>A</u> TGTGATGA	1268
Cystic fibrosis Gly149Arg GGA to AGA	CTTCTCTTTATTGTGAGGACACTGCTCCTACACCCAGCCATTT TTGGCCTTCATCACATT <u>G</u> GGAATGCAGATGAGAATAGCTATGTT TAGTTTGATTATAAGAAGGTAATACTTCCTTGCA	1269
	TGCAAGGAAGTATTACCTTCTTATAAATCAAACAACTAAACATAGC TATTCTCATCTGCATTCCA <u>A</u> TGTGATGAAGGCCAAAAATGGCT GGGTGTAGGAGCAGTGTCTCACAATAAAGAGAAG	1270
	ATCACATT <u>G</u> GGAATGCAG	1271
	CTGCATTCCA <u>A</u> TGTGAT	1272

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Gln151Term CAG to TAG	TTTATTGTGAGGACACTGCTCCTACACCCAGCCATTTTGGC CTTCATCACATTGGAATGCAGATGAGAATAGCTATGTTTAGTT TGATTATAAGAAGGTAATACTTCCTTGCACAGGCC	1273
	GGCCTGTGCAAGGAAGTATTACCTTCTTATAAATCAAATAAA CATAGCTATTCTCATCTGCATTCCAATGTGATGAAGGCCAAAA ATGGCTGGGTGTAGGAGCAGTGCCTCACAATAAA	1274
	TTGGAATGCAGATGAGA	1275
	TCTCATCTGCATTCCAA	1276
Cystic fibrosis Lys166Glu AAG-GAG	AATATATTTGTATTTTGTGTTGAAATTATCTAAGTTTCCATTT TTCTTTTAGACTTTAAAGCTGTCAAGCCGTGTTCTAGATAAAA TAAGTATTGGACAACTTGTTAGTCTCCTTTCCA	1277
	TGGAAAGGAGACTAACAAGTTGTCCAATACTTATTTTATCTAG AACACGGCTTGACAGCTTTAAAGTCTAAAAGAAAAATGGAAA GTTAGATAATTTCAACAAACAAAATACAAATATATT	1278
	AGACTTTAAAGCTGTCA	1279
	TGACAGCTTTAAAGTCT	1280
Cystic fibrosis Ile175Val ATA-GTA	TTATCTAAGTTTCCATTTTCTTTTAGACTTTAAAGCTGTCAAG CCGTGTTCTAGATAAAAATAAGTATTGGACAACTTGTTAGTCTC CTTTCCAACAACCTGAACAAATTTGATGAAGTAT	1281
	ATACTTCATCAAATTTGTTTCAAGTTGTTGGAAAGGAGACTAAC AAGTTGTCCAATACTTATTTTATCTAGAACACGGCTTGACAGC TTTAAAGTCTAAAAGAAAAATGGAAAGTTAGATAA	1282
	TAGATAAAAATAAGTATT	1283
	AATACTTATTTTATCTA	1284
Cystic fibrosis Gly178Arg GGA to AGA	TTTCCATTTTCTTTTAGACTTTAAAGCTGTCAAGCCGTGTTCT AGATAAAATAAGTATTGGACAACTTGTTAGTCTCCTTTCCAAC AACCTGAACAAATTTGATGAAGTATGTACCTATT	1285
	AATAGGTACATACTTCATCAAATTTGTTTCAAGTTGTTGGAAAG GAGACTAACAAGTTGTCCAATACTTATTTTATCTAGAACACGG CTTGACAGCTTTAAAGTCTAAAAGAAAAATGGAAA	1286
	TAAGTATTGGACAACTT	1287
	AAGTTGTCCAATACTTA	1288
Cystic fibrosis His199Gln CAT to CAG	AAGATACAATGACACCTGTTTTTGCTGTGCTTTTATTTTCCAG GGACTTGCAATTGGCACATTTCTGTGGATCGCTCCTTTGCAA GTGGCACTCCTCATGGGGCTAATCTGGGAGTTGTTA	1289

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAACAACTCCCAGATTAGCCCCATGAGGAGTGCCACTTGCAA AGGAGCGATCCACACGAAATGTGCCAATGCAAGTCCCTGGA AAATAAAAGCACAGCAAAAACAGGTGTCATTGTATCTT	1290
	TTGGCACATTTTCGTGTG	1291
	CACACGAAATGTGCCAA	1292
Cystic fibrosis His199Tyr CAT to TAT	GGAAGATACAATGACACCTGTTTTGCTGTGCTTTATTTTCC AGGGACTTGCAATTGGCAATTTCGTGTGGATCGCTCCTTTGC AAGTGGCACTCCTCATGGGGCTAATCTGGGAGTTGT	1293
	ACAACTCCCAGATTAGCCCCATGAGGAGTGCCACTTGCAAAG GAGCGATCCACACGAAATGTGCCAATGCAAGTCCCTGGA ATAAAAGCACAGCAAAAACAGGTGTCATTGTATCTTCC	1294
	CATTGGCAATTTCGTG	1295
	CACGAAATGTGCCAATG	1296
Cystic fibrosis Pro205Ser CCT to TCT	TGTTTTGCTGTGCTTTATTTTCCAGGGACTTGCAATTGGCAC ATTCGTGTGGATCGCTCCTTTGCAAGTGGCACTCCTCATGG GGCTAATCTGGGAGTTGTTACAGGCGTCTGCCTTCT	1297
	AGAAGGCAGACGCCTGTAACAACTCCCAGATTAGCCCCATG AGGAGTGCCACTTGCAAAGGAGCGATCCACACGAAATGTGC CAATGCAAGTCCCTGGAATAAAAGCACAGCAAAAACA	1298
	GGATCGCTCCTTTGCAA	1299
	TTGCAAAGGAGCGATCC	1300
Cystic fibrosis Leu206Trp TTG to TGG	TTTGCTGTGCTTTATTTTCCAGGGACTTGCAATTGGCACATTT CGTGTGGATCGCTCCTTTGCAAGTGGCACTCCTCATGGGGC TAATCTGGGAGTTGTTACAGGCGTCTGCCTTCTGTGG	1301
	CCACAGAAGGCAGACGCCTGTAACAACTCCCAGATTAGCCC CATGAGGAGTGCCACTTGCAAAGGAGCGATCCACACGAAAT GTGCCAATGCAAGTCCCTGGAATAAAAGCACAGCAAAA	1302
	CGCTCCTTTGCAAGTGG	1303
	CCACTTGCAAAGGAGCG	1304
Cystic fibrosis Gln220Term CAG to TAG	TTCGTGTGGATCGCTCCTTTGCAAGTGGCACTCCTCATGGG GCTAATCTGGGAGTTGTTACAGGCGTCTGCCTTCTGTGGACT TGGTTTCCTGATAGTCCTTGCCCTTTTTCAGGCTGGGC	1305
	GCCCAGCCTGAAAAAGGGCAAGGACTATCAGGAAACCAAGT CCACAGAAGGCAGACGCCTGTAACAACTCCCAGATTAGCCC CATGAGGAGTGCCACTTGCAAAGGAGCGATCCACACGAA	1306

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGTTGTTA <u>C</u> AGGCGTCT	1307
	AGACGCCT <u>G</u> TAACAACT	1308
Cystic fibrosis Cys225Arg TGT-CGT	CCTTTGCAAGTGGCACTCCTCATGGGGCTAATCTGGGAGTT GTTACAGGCGTCTGCCTT <u>C</u> TGTGGACTTGGTTTCCTGATAGT CCTTGCCCTTTTTT CAGGCTGGGCTAGGGAGAATGATGA	1309
	TCATCATTCTCCCTAGCCCAGCCTGAAAAAGGGCAAGGACTA TCAGGAAACCAAGTCCACA <u>A</u> GAAGGCAGACGCCTGTAACAAC TCCCAGATTAGCCCCATGAGGAGTGCCACTTGCAAAGG	1310
	CTGCCTT <u>C</u> TGTGGACTT	1311
	AAGTCCACA <u>G</u> AAGGCAG	1312
Cystic fibrosis Val232Asp GTC to GAC	TGGGGCTAATCTGGGAGTTGTTACAGGCGTCTGCCTTCTGT GGACTTGGTTTCCTGATAGT <u>C</u> CTTGCCCTTTTT CAGGCTGGG CTAGGGAGAATGATGATGAAGTACAGGTAGCAACCTAT	1313
	ATAGGTTGCTACCTGTACTTCATCATCATTCTCCCTAGCCCA GCCTGAAAAAGGGCAAGG <u>A</u> CTATCAGGAAACCAAGTCCACA GAAGGCAGACGCCTGTAACAACCTCCCAGATTAGCCCCA	1314
	CCTGATAGT <u>C</u> CTTGCCC	1315
	GGGCAAGG <u>A</u> CTATCAGG	1316
Cystic fibrosis Gly239Arg GGG to AGG	GTTACAGGCGTCTGCCTTCTGTGGACTTGGTTTCCTGATAGT CCTTGCCCTTTTTT CAGGCTGGGCTAGGGAGAATGATGATGAA GTACAGGTAGCAACCTATTTTCATAACTTGAAAGTTT	1317
	AACTTTCAAGTTATGAAAATAGGTTGCTACCTGTACTTCATC ATCATTCTCCCTAGCCC <u>A</u> GCCTGAAAAAGGGCAAGGACTATC AGGAAACCAAGTCCACAGAAGGCAGACGCCTGTAAC	1318
	TTTCAGGCTGGGCTAGG	1319
	CCTAGCCCAGCCTGAAA	1320

EXAMPLE 10
Cyclin-dependent kinase inhibitor 2A - CDKN2A

The human CDKN2A gene was also designated MTS-1 for multiple tumor suppressor-1 and has been implicated in multiple cancers including, for example, malignant melanoma. Malignant melanoma is a cutaneous neoplasm of melanocytes. Melanomas generally have features of asymmetry, irregular border, variegated color, and diameter greater than 6 mm. The precise cause of melanoma is

unknown, but sunlight and heredity are risk factors. Melanoma has been increasing during the past few decades.

The CDKN2A gene has been found to be homozygously deleted at high frequency in cell lines derived from tumors of lung, breast, brain, bone, skin, bladder, kidney, ovary, and lymphocyte.

- 5 Melanoma cell lines carried at least one copy of CDKN2A in combination with a deleted allele. Melanoma cell lines that carried at least 1 copy of CDKN2A frequently showed nonsense, missense, or frameshift mutations in the gene. Thus, CDKN2A may rival p53 (see Example 5) in the universality of its involvement in tumorigenesis. The attached table discloses the correcting oligonucleotide base sequences for the CDKN2A oligonucleotides of the invention.

Table 17
CDKN2A Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Melanoma Trp15Term TGG-TAG	GGGCGGCGGGGAGCAGCATGGAGCCGGCGGGGAGCAGCATGGAGCCTTCGGCTGACTGGCTGGCCACGGCCGCGGCCCGGGGTCTGGGTAGAGGAGGTGCGGGCGCTGCTGGAGGCGGG	1321
	CCCGCCTCCAGCAGCGCCCGCACCTCCTCTACCCGACCCCGGGCCGCGGCCGTGGCCAGCCAGTCAGCCGAAGGCTCCATGCTGCTCCCCGCCGCCGGCTCCATGCTGCTCCCCGCCGCC	1322
	GGCTGACTGGCTGGCCA	1323
	TGGCCAGCCAGTCAGCC	1324
Melanoma Leu16Pro CTG-CCG	CGGCGGGGAGCAGCATGGAGCCGGCGGGGAGCAGCATGGAGCCTTCGGCTGACTGGCTGGCCACGGCCGCGGCCCGGGGTCTGGGTAGAGGAGGTGCGGGCGCTGCTGGAGGCGGGGGC	1325
	GCCCCCGCCTCCAGCAGCGCCCGCACCTCCTCTACCCGACCCCGGGGCCGCGGCCGTGGCCAGCCAGTCAGCCGAAGGCTCCATGCTGCTCCCCGCCGCCGGCTCCATGCTGCTCCCCGCCCG	1326
	TGACTGGCTGGCCACGG	1327
	CCGTGGCCAGCCAGTCA	1328
Melanoma Gly23Asp GGT-GAT	CGGCGGGCGGGGAGCAGCATGGAGCCTTCGGCTGACTGGCTGGCCACGGCCGCGGCCCGGGGTCTGGGTAGAGGAGGTGCGGGCGCTGCTGGAGGCGGGGGCGCTGCCAACGCACCGAATAG	1329
	CTATTCGGTGCGTTGGGCAGCGCCCCCGCCTCCAGCAGCGCCGACCTCCTCTACCCGAGCCCGGGGCCGCGGCCGGGCCAGTCAGCCGAAGGCTCCATGCTGCTCCCCGCCGCC	1330
	GGCCCCGGGTCGGGTAG	1331

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CTACCCGACCCCGGGCC	1332
Melanoma Arg24Pro CGG-CCG	CGGCGGGGAGCAGCATGGAGCCTTCGGCTGACTGGCTGGCC ACGGCCGCGGCCCGGGGTCGGGTAGAGGAGGTGCGGGCGC TGCTGGAGGCGGGGGCGCTGCCAACGCACCGAATAGTTA	1333
	TAACTATTCGGTGCGTTGGGCAGCGCCCCGCCTCCAGCAGC GCCCCGACCTCCTCTACCCGACCCCGGGCCGCGGCCGTGGC CAGCCAGTCAGCCGAAGGCTCCATGCTGCTCCCCGCCG	1334
	CCGGGGTCCGGGTAGAGG	1335
	CCTCTACCCGACCCCGG	1336
Melanoma Leu32Pro CTG-CCG	CGGCTGACTGGCTGGCCACGGCCGCGGCCCGGGGTCTGGGT AGAGGAGGTGCGGGCGCTGCTGGAGGCGGGGGCGCTGCCC AACGCACCGAATAGTTACGGTCGGAGGCCGATCCAGGTGGG	1337
	CCCACCTGGATCGGCCTCCGACCGTAACTATTCGGTGCGTTG GGCAGCGCCCCCGCCTCCAGCAGCGCCCGCACCTCCTCTAC CCGACCCCGGGCCGCGGCCGTGGCCAGCCAGTCAGCCG	1338
	GGCGCTGCTGGAGGCGG	1339
	CCGCCTCCAGCAGCGCC	1340
Melanoma Gly35Ala GGG-GCG	GGCTGGCCACGGCCGCGGCCCGGGGTCTGGGTAGAGGAGGT GCGGGCGCTGCTGGAGGCGGGGGCGCTGCCAACGCACCG AATAGTTACGGTCGGAGGCCGATCCAGGTGGGTAGAGGGTC	1341
	GACCCTCTACCCACCTGGATCGGCCTCCGACCGTAACTATTC GGTGCGTTGGGCAGCGCCCGGCCTCCAGCAGCGCCCGCAC CTCCTCTACCCGACCCCGGGCCGCGGCCGTGGCCAGCC	1342
	GGAGGCGGGGGCGCTGC	1343
	GCAGCGCCCGGCCTCC	1344
Melanoma Tyr44Term TACg-TAA	GGTAGAGGAGGTGCGGGCGCTGCTGGAGGCGGGGGCGCTG CCCAACGCACCGAATAGTTACGGTCGGAGGCCGATCCAGGTG GGTAGAGGGTCTGCAGCGGGAGCAGGGGATGGCGGGCGA	1345
	TCGCCCCCATCCCCTGCTCCCGCTGCAGACCCTCTACCCAC CTGGATCGGCCTCCGACCGTAACTATTCGGTGCGTTGGGCAG CGCCCCCGCCTCCAGCAGCGCCCGCACCTCCTCTACC	1346
	AATAGTTACGGTCGGAG	1347
	CTCCGACCGTAACTATT	1348
Melanoma Met53Ile ATGa-ATC	TCTCCCATACCTGCCCCACCCCTGGCTCTGACCACTCTGCTC TCTCTGGCAGGTCATGATGATGGGCAGCGCCCGCGTGCGG AGCTGCTGCTGCTCCACGGCGCGGAGCCCAACTGCGCA	1349
	TGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCTCCG CCACGCGGGCGCTGCCCATCATCATGACCTGCCAGAGAGAG CAGAGTGGTCAGAGCCAGGTGGGGGCAGGTATGGGAGA	1350
	GTCATGATGATGGGCAG	1351

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CTGCCCATCATCATGAC	1352
Melanoma Met54Ile ATGg-ATT	CCCATACCTGCCCCACCCTGGCTCTGACCACTCTGCTCTCTCTGGCAGGTCATGATGATGGGCAGCGCCCCGCTGGCGGAGCTGCTGCTGCTCCACGGCGCGGAGCCCCAACTGCGCAGAC	1353
	GTCTGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCTCCGCCACGCGGGCGCTGCCCATCATCATGACCTGCCAGAGA GAGCAGAGTGGTCAGAGCCAGGGTGGGGGCAGGTATGGG	1354
	ATGATGATGGGCAGCGC	1355
	GCGCTGCCCCATCATCAT	1356
Melanoma Ser56Ile AGC-ATC	GCCGGCCCCCACCCTGGCTCTGACCACTTCTGTTCTCTCTGGCAGGTCATGATGATGGGCAAGCGCCCGAGTGGCGGAGCTGCTGCTGCTCCACGGCGCGGAGCCCCAACTGCGCCGACCCCGC	1357
	GCGGGGTGCGGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCTCCGCCACTCGGGCGCTGCCCATCATCATGACCTGCCAGAGAGAACAGAATGGTCAGAGCCAGGGTGGGGGCCCGGC	1358
	GATGGGCAGCGCCCGAG	1359
	CTCGGGCGCTGCCCATC	1360
Melanoma Ala57Val GCC-GTC	GGCCCCCACCCTGGCTCTGACCACTTCTGTTCTCTCTGGCAGGTCATGATGATGGGCAGCGCCCGAGTGGCGGAGCTGCTGCTGCTCCACGGCGCGGAGCCCCAACTGCGCCGACCCCGCCAC	1361
	GTGGCGGGGTGCGGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCTCCGCCACTCGGGCGCTGCCCATCATCATGACCTGCCAGAGAGAACAGAATGGTCAGAGCCAGGGTGGGGGCC	1362
	GGGCAGCGCCCGAGTGG	1363
	CCACTCGGGCGCTGCCC	1364
Melanoma Arg58Term cCGA-TGA	CCCCCACCCTGGCTCTGACCACTTCTGTTCTCTCTGGCAGGTCATGATGATGGGCAGCGCCCGAGTGGCGGAGCTGCTGCTGCTCCACGGCGCGGAGCCCCAACTGCGCCGACCCCGCCACTC	1365
	GAGTGGCGGGGTGCGGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCTCCGCCACTCGGGCGCTGCCCATCATCATGACCTGCCAGAGAGAACAGAATGGTCAGAGCCAGGGTGGGGG	1366
	GCAGCGCCCGAGTGGCG	1367
	CGCCACTCGGGCGCTGC	1368
Melanoma Val59Gly GTG-GGG	CACCCTGGCTCTGACCACTTCTGTTCTCTCTGGCAGGTCATGATGATGGGCAGCGCCCGAGTGGCGGAGCTGCTGCTGCTCCACGGCGGAGCCCCAACTGCGCCGACCCCGCCACTCTCAC	1369
	GTGAGAGTGGCGGGGTGCGGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCTCCGCCACTCGGGCGCTGCCCATCATCATGACCTGCCAGAGAGAACAGAATGGTCAGAGCCAGGGTG	1370
	CGCCCGAGTGGCGGAGC	1371

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCTCCGCCACTCGGGCG	1372
Melanoma Leu62Pro CTG-CCG	TCTGACCACTCTGCTCTCTCTGGCAGGTCATGATGATGGGCA GCGCCCGCGTGGCGGAGCTGCTGCTGCTCCACGGCGCGGA GCCCAACTGCGCAGACCCTGCCACTCTCACCCGACCGGT	1373
	ACCGGTCGGGTGAGAGTGGCAGGGTCTGCGCAGTTGGGCTC CGCGCCGTGGAGCAGCAGCAGCTCCGCCACGCGGGCGCTG CCCATCATCATGACCTGCCAGAGAGAGCAGAGTGGTCAGA	1374
	GGCGGAGCTGCTGCTGC	1375
	GCAGCAGCAGCTCCGCC	1376
Melanoma Ala68Val GCG-GTG	TCTGGCAGGTCATGATGATGGGCAGCGCCCGCGTGGCGGAG CTGCTGCTGCTCCACGGCGCGGAGCCCAACTGCGCAGACCC TGCCACTCTACCCGACCGGTGCATGATGCTGCCCGGGA	1377
	TCCCGGGCAGCATCATGCACCGGTCGGGTGAGAGTGGCAGG GTCTGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCT CCGCCACGCGGGCGCTGCCATCATCATGACCTGCCAGA	1378
	CCACGGCGCGGAGCCCA	1379
	TGGGCTCCGCGCCGTGG	1380
Melanoma Asn71Lys AACT-AAA	CATGATGATGGGCAGCGCCCGAGTGGCGGAGCTGCTGCTGC TCCACGGCGCGGAGCCCAACTGCGCCGACCCCGCCACTCTC ACCCGACCCGTGCACGACGCTGCCCGGGAGGGCTTCCTG	1381
	CAGGAAGCCCTCCCGGGCAGCGTCGTGCACGGGTGCGGTGA GAGTGGCGGGGTGCGCGCAGTTGGGCTCCGCGCCGTGGAG CAGCAGCAGCTCCGCCACTCGGGCGCTGCCATCATCATG	1382
	GAGCCCAACTGCGCCGA	1383
	TCGGCGCAGTTGGGCTC	1384
Melanoma Asn71Ser AAC-AGC	TCATGATGATGGGCAGCGCCCGAGTGGCGGAGCTGCTGCTG CTCCACGGCGCGGAGCCCAACTGCGCCGACCCCGCCACTCT CACCCGACCCGTGCACGACGCTGCCCGGGAGGGCTTCCT	1385
	AGGAAGCCCTCCCGGGCAGCGTCGTGCACGGGTGCGGTGAG AGTGGCGGGGTGCGCGCAGTTGGGCTCCGCGCCGTGGAGCA GCAGCAGCTCCGCCACTCGGGCGCTGCCATCATCATGA	1386
	GGAGCCCAACTGCGCCG	1387
	CGGCGCAGTTGGGCTCC	1388
Melanoma Pro81Leu CCC-CTC	AGCTGCTGCTGCTCCACGGCGCGGAGCCCAACTGCGCCGAC CCCGCCACTCTACCCGACCGGTGCACGACGCTGCCCGGGA GGGCTTCCTGGACACGCTGGTGGTGTGTCACCGGGCCGG	1389
	CCGGCCCGGTGCAGCACCACCAGCGTGTCCAGGAAGCCCTC CCGCGCAGCGTCGTGCACGGGTGCGGTGAGAGTGGCGGGG TCGGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCT	1390
	CACCCGACCGGTGCACG	1391

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGTGCACGGGTCGGGTG	1392
Melanoma Asp84Tyr cGAC-TAC	CTGCTCCACGGCGCGGAGCCCAACTGCGCCGACCCCGCCAC TCTACCCGACCCGTGCACGACGCTGCCCGGAGGGCTTCC TGGACACGCTGGTGGTGTCTGCACCGGGCCGGGGCGCGGC	1393
	GCCGCGCCCCGGCCCGGTGCAGCACCACCAGCGTGTCCAGG AAGCCCTCCCGGGCAGCGTCTGTGCACGGGTCTGGGTGAGAGT GGCGGGGTCTGGCGCAGTTGGGCTCCGCGCCGTGGAGCAG	1394
	CCGTGCACGACGCTGCC	1395
	GGCAGCGTCTGTGCACGG	1396
Melanoma Ala85Thr cGCT-ACT	CTCCACGGCGCGGAGCCCAACTGCGCCGACCCCGCCACTCT CACCCGACCCGTGCACGACGCTGCCCGGAGGGCTTCTCTGG ACACGCTGGTGGTGTCTGCACCGGGCCGGGGCGCGGCTGG	1397
	CCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAGCGTGTCC AGGAAGCCCTCCCGGGCAGCGTCTGTGCACGGGTCTGGGTGAG AGTGGCGGGGTCTGGCGCAGTTGGGCTCCGCGCCGTGGAG	1398
	TGCACGACGCTGCCCGG	1399
	CCGGGCAGCGTCTGTGCA	1400
Melanoma Arg87Pro CGG-CCG	GCGCGGAGCCCAACTGCGCCGACCCCGCCACTCTCACC CGA CCCGTGCACGACGCTGCCCGGGAGGGCTTCTCTGGACACGCT GGTGGTGTCTGCACCGGGCCGGGGCGCGGCTGGACGTGCG	1401
	CGCACGTCCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAG CGTGTCCAGGAAGCCCTCCCGGGCAGCGTCTGTGCACGGGTCT GGGTGAGAGTGGCGGGGTCTGGCGCAGTTGGGCTCCGCGCC	1402
	CGCTGCCCGGGAGGGCT	1403
	AGCCCTCCCGGGCAGCG	1404
Melanoma Arg87Trp cCGG-TGG	GGCGCGGAGCCCAACTGCGCCGACCCCGCCACTCTCACC CG ACCCGTGCACGACGCTGCCCGGGAGGGCTTCTCTGGACACGC TGGTGGTGTCTGCACCGGGCCGGGGCGCGGCTGGACGTGC	1405
	GCACGTCCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAGC GTGTCCAGGAAGCCCTCCCGGGCAGCGTCTGTGCACGGGTCTG GGTGAGAGTGGCGGGGTCTGGCGCAGTTGGGCTCCGCGCC	1406
	ACGCTGCCCGGGAGGGC	1407
	GCCCTCCCGGGCAGCGT	1408
Melanoma Leu97Arg CTG-CGG	CTCTACCCGACCGGTGCATGATGCTGCCCGGGAGGGCTTC CTGGACACGCTGGTGGTGTCTGCACCGGGCCGGGGCGCGGCT GGACGTGCGGATGCCTGGGGTCTGTCTGCCCGTGGACTT	1409
	AAGTCCACGGGCAGACGACCCAGGCATCGCGCACGTCCAG CCGCGCCCCGGCCCGGTCTCTGCACACCACCAGCGTGTCCAGGA AGCCCTCCCGGGCAGCATCATGCACCGGTCTGGGTGAGAG	1410
	GGTGGTGTCTGCACCGGG	1411

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CCCGGTGCAGCACCACC	1412
Melanoma Arg99Pro CGG-CCG	CCCGACCGGTGCATGATGCTGCCCGGGAGGGCTTCCTGGAC ACGCTGGTGGTGTGTCACCGGGCCGGGCGCGGCTGGACG TGCGCGATGCCTGGGGTCGTCTGCCCGTGGACTTGGCCGA	1413
	TCGGCCAAGTCCACGGGCAGACGACCCAGGCATCGCGCAC GTCCAGCCGCGCCCCGGCCGGGTGCAGCACCACCAGCGTGT CCAGGAAGCCCTCCCGGGCAGCATCATGCACCGGTCCGG	1414
	GCTGCACCGGGCCGGG	1415
	CCCCGGCCCGGTGCAGC	1416
Melanoma Gly101Trp cGGG-TGG	CCGGTGCATGATGCTGCCCGGGAGGGCTTCCTGGACACGCT GGTGGTGTGTCACCGGGCCGGGCGCGGCTGGACGTGCGC GATGCCTGGGGTCGTCTGCCCGTGGACTTGGCCGAGGAGC	1417
	GCTCCTCGGCCAAGTCCACGGGCAGACGACCCAGGCATCG CGCACGTCCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAG CGTGTCCAGGAAGCCCTCCCGGGCAGCATCATGCACCGG	1418
	ACCGGGCCGGGGCGCGG	1419
	CCGCGCCCCGGCCCGGT	1420
Melanoma Arg107Cys gCGC-TGC	CGGGAGGGCTTCCTGGACACGCTGGTGGTGTGTCACCGGGC CGGGGCGCGGCTGGACGTGCGCGATGCCTGGGGTCGTCTGC CCGTGGACTTGGCCGAGGAGCGGGGCCACCGCGACGTTG	1421
	CAACGTCGCGGTGGCCCCGCTCCTCGGCCAAGTCCACGGGC AGACGACCCAGGCATCGCGCACGTCCAGCCGCGCCCCGGC CCGGTGCAGCACCACCAGCGTGTCCAGGAAGCCCTCCCG	1422
	TGGACGTGCGCGATGCC	1423
	GGCATCGCGCACGTCCA	1424
Melanoma Ala118Thr gGCT-ACT	CACCGGGCCGGGGCGCGGCTGGACGTGCGCGATGCCTGGG GCCGTCTGCCCGTGGACCTGGCTGAGGAGCTGGGCCATCGC GATGTGCGACGGTACCTGCGCGCGGCTGCGGGGGGCACCA	1425
	TGGTGCCCCCGCAGCCGCGCGCAGGTACCGTGCGACATCG CGATGGCCAGCTCCTCAGCCAGGTCCACGGGCAGACGGCC CCAGGCATCGCGCACGTCCAGCCGCGCCCCGGCCCGGTG	1426
	TGGACCTGGCTGAGGAG	1427
	CTCCTCAGCCAGGTCCA	1428
Melanoma Val126Asp GTC-GAC	TGCGCGATGCCTGGGGCCGTCTGCCCGTGGACCTGGCTGAG GAGCTGGGCCATCGCGATGTCGCACGGTACCTGCGCGCGGC TGCGGGGGGCACCAGAGGCAGTAACCATGCCCGCATAGA	1429
	TCTATGCGGGCATGGTACTGCCTCTGGTGCCCCCGCAGCC GCGCGCAGGTACCGTGCGACATCGCGATGGCCCACTCTCTC AGCCAGGTCCACGGGCAGACGGCCCCAGGCATCGCGCA	1430
	TCGCGATGTCGCACGGT	1431

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ACCGTGCGACATCGCGA	1432

EXAMPLE 11
Adenomatous polyposis of the colon - APC

Adenomatous polyposis of the colon is characterized by adenomatous polyps of the colon and rectum; in extreme cases the bowel is carpeted with a myriad of polyps. This is a viciously premalignant disease with one or more polyps progressing through dysplasia to malignancy in untreated gene carriers with a median age at diagnosis of 40 years.

Mutations in the APC gene are an initiating event for both familial and sporadic colorectal tumorigenesis and many alleles of the APC gene have been identified. Carcinoma may arise at any age from late childhood through the seventh decade with presenting features including, for example, weight loss and inanition, bowel obstruction, or bloody diarrhea. Cases of new mutation still present in these ways but in areas with well organized registers most other gene carriers are detected. The attached table discloses the correcting oligonucleotide base sequences for the APC oligonucleotides of the invention.

Table 18
APC Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Arg121Term AGA-TGA	GGATCTGTATCAAGCCGTTCTGGAGAGTGCAGTCCTGTTCTT ATGGGTTTCATTTCCAAGAAGAGGGTTTGTAAATGGAAGCAGA GAAAGTACTGGATATTTAGAAGAACTTGAGAAAGAGA	1433
	TCTCTTTCTCAAGTTCTTCTAAATATCCAGTACTTTCTCTGCTT CCATTTACAAACCCTCTTCTTGAAATGAACCCATAGGAACAG GACTGCACTCTCCAGAACGGCTTGATACAGATCC	1434
	TTCCAAGAAGAGGGTTT	1435
	AAACCCTCTTCTTGAA	1436
Adenomatous polyposis coli Trp157Term TGG-TAG	AAAAAAAAAATAGGTCATTGCTTCTTGCTGATCTTGACAAAGAA GAAAAGGAAAAAGACTGGTATTACGCTCAACTTCAGAATCTCA CTAAAAGAATAGATAGTCTTCCTTTAACTGAAAA	1437
	TTTTCAAGTTAAAGGAAGACTATCTATTCTTTAGTGAGATTCTG AAGTTGAGCGTAATACAGTCTTTTTCTTTCTTTCTTTGTCAA GATCAGCAAGAAGCAATGACCTATTTTTTTTTT	1438
	AAAAGACTGGTATTACG	1439
	CGTAATACAGTCTTTT	1440
Adenomatous polyposis coli Tyr159Term TAC-TAG	AAATAGGTCATTGCTTCTTGCTGATCTTGACAAAGAAGAAAAG GAAAAGACTGGTATTACGCTCAACTTCAGAATCTCACTAAAA GAATAGATAGTCTTCCTTTAACTGAAAATGTAAGT	1441
	ACTTACATTTTCAGTTAAAGGAAGACTATCTATTCTTTTAGTGA GATTCTGAAGTTGAGCGTAATACAGTCTTTTTCTTTCTTTCTTCT TTGTCAAGATCAGCAAGAAGCAATGACCTATTT	1442
	TGGTATTACGCTCAACT	1443
	AGTTGAGCGTAATACCA	1444
Adenomatous polyposis coli Gln163Term CAG-TAG	TTGCTTCTTGCTGATCTTGACAAAGAAGAAAAGGAAAAAGACT GGTATTACGCTCAACTTCAGAATCTCACTAAAAGAATAGATAG TCTTCCTTTAACTGAAAATGTAAGTAACTGGCAGT	1445
	ACTGCCAGTTACTTACATTTTCAGTTAAAGGAAGACTATCTATT CTTTTAGTGAGATTCTGAAGTTGAGCGTAATACAGTCTTTTTCT CTTTCTTCTTTGTCAAGATCAGCAAGAAGCAA	1446
	CTCAACTTCAGAATCTC	1447
	GAGATTCTGAAGTTGAG	1448
Adenomatous polyposis coli Arg168Term AGA-TGA	CTTGACAAAGAAGAAAAGGAAAAAGACTGGTATTACGCTCAAC TTCAGAATCTCACTAAAAGAATAGATAGTCTTCCTTTAACTGAA AATGTAAGTAACTGGCAGTACAACCTATTTGAAA	1449
	TTTCAAATAAGTTGTAAGTCCAGTACTTACATTTTCAGTTAAA GGAAGACTATCTATTCTTTAGTGAGATTCTGAAGTTGAGCGT AATACCAGTCTTTTTCTTTCTTTCTTTGTCAAG	1450

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TCACTAAAAGAATAGAT	1451
	ATCTATTCITTTAGTGA	1452
Adenomatous polyposis coli Ser171Ile AGT-ATT	AAGAAAAGGAAAAAGACTGGTATTACGCTCAACTTCAGAATCT CACTAAAAGAATAGATAGTCTTCCTTTAACTGAAAATGTAAGTA ACTGGCAGTACAACCTATTGAACTTTAATAAC	1453
	GTTATTAAAGTTTCAAATAAGTTGACTGCCAGTTACTTACATT TTCAGTTAAAGGAAGACTATCTATTCTTTTAGTGAGATTCTGAA GTTGAGCGTAATACCAGTCTTTTCCTTTCTT	1454
	AATAGATAGTCTTCCTT	1455
	AAGGAAGACTATCTATT	1456
Adenomatous polyposis coli Gln181Term CAA-TAA	GATTAACGTAATAACAAGATATTGATACTTTTTATTATTTGTGG TTTTAGTTTTCTTACAACAGATATGACCAGAAGGCAATTGG AATATGAAGCAAGGCAAATCAGAGTTGCGATGG	1457
	CCATCGCAACTCTGATTTGCCTTGCTTCATATTCCAATTGCCT TCTGGTCATATCTGTTTGAAGGAAAACAAAACCACAAATAAT AAAAAAGTATCAATATCTTGATTTACGTTAATC	1458
	TTTCCTTACAAACAGAT	1459
	ATCTGTTTGAAGGAAA	1460
Adenomatous polyposis coli Glu190Term GAA-TAA	CTTTTTTATTATTTGTGGTTTTAGTTTTCTTACAACAGATATG ACCAGAAGGCAATTGGAATATGAAGCAAGGCAAATCAGAGTT GCGATGGAAGAACAACCTAGGTACCTGCCAGGATA	1461
	TATCCTGGCAGGTACCTAGTTGTTCTTCCATCGCAACTCTGAT TTGCCCTTGCTTCATATTCCAATTGCCTTCTGGTCATATCTGTTT GTAAGGAAAACAAAACCACAAATAATAAAAAAG	1462
	GGCAATTGGAATATGAA	1463
	TTCATATTCCAATTGCC	1464
Adenomatous polyposis coli Gln208Term CAG-TAG	CAATTGGAATATGAAGCAAGGCAAATCAGAGTTGCGATGGAA GAACAACCTAGGTACCTGCCAGGATATGGAAAAACGAGCACAG GTAAGTTACTTGTTTCTAAGTGATAAAACAGCGAAGA	1465
	TCTTCGCTGTTTTATCACTTAGAAACAAGTAACCTGTGCT CGTTTTTCCATATCCTGGCAGGTACCTAGTTGTTCTTCCATCG CAACTCTGATTTGCCTTGCTTCATATTCCAATTG	1466
	GTACCTGCCAGGATATG	1467
	CATATCCTGGCAGGTAC	1468
Adenomatous polyposis coli Arg213Term CGA-TGA	GCAAGGCAAATCAGAGTTGCGATGGAAGAACAACCTAGGTACC TGCCAGGATATGGAAAAACGAGCACAGGTAAGTTACTTGTTTC TAAGTGATAAAACAGCGAAGAGCTATTAGGAATAAA	1469
	TTTATTCCTAATAGCTCTTCGCTGTTTTATCACTTAGAAACAAG TAACTTACCTGTGCTCGTTTTTCCATATCCTGGCAGGTACCTA GTTGTTCTTCCATCGCAACTCTGATTTGCCTTGC	1470
	TGGAAAAACGAGCACAG	1471
	CTGTGCTCGTTTTTCCA	1472

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Arg232Term CGA-TGA	GTTTTATTTTAGCGAAGAATAGCCAGAATTCAGCAAATCGAAA AGGACATACTTCGTATACGACAGCTTTTACAGTCCCAAGCAAC AGAAGCAGAGGTTAGTAAATTGCCTTTCTTGTTTG	1473
	CAAACAAGAAAGGCAATTTACTAACCTCTGCTTCTGTTGCTTG GGACTGTAAAAGCTGTCGTATACGAAGTATGTCCTTTTCGATT TGCTGAATTCTGGCTATTCTTCGCTAAAATAAAAC	1474
	TTCGTATACGACAGCTT	1475
	AAGCTGTCGTATACGAA	1476
Adenomatous polyposis coli Gln233Term CAG-TAG	TTATTTTAGCGAAGAATAGCCAGAATTCAGCAAATCGAAAAGG ACATACTTCGTATACGACAGCTTTTACAGTCCCAAGCAACAGA AGCAGAGGTTAGTAAATTGCCTTTCTTGTTTGTTG	1477
	CCACAAACAAGAAAGGCAATTTACTAACCTCTGCTTCTGTTGC TTGGGACTGTAAAAGCTGTCGTATACGAAGTATGTCCTTTTCG ATTTGCTGAATTCTGGCTATTCTTCGCTAAAATAA	1478
	GTATACGACAGCTTTTA	1479
	TAAAAGCTGTCGTATAC	1480
Adenomatous polyposis coli Gln247Term CAG-TAG	AGAAAGCCTACACCATTTTTGCATGTACTGATGTTAACTCCAT CTTAACAGAGGTCATCTCAGAACAAAGCATGAAACCGGCTCAC ATGATGCTGAGCGGCAGAATGAAGGTCAAGGAGTGG	1481
	CCACTCCTTGACCTTCATTCTGCCGCTCAGCATCATGTGAGC CGGTTTCATGCTTGTCTGAGATGACCTCTGTTAAGATGGAGT TAACATCAGTACATGCAAAAATGGTGTAGGCTTTCT	1482
	GGTCATCTCAGAACAAAG	1483
	CTTGTTCTGAGATGACC	1484
Adenomatous polyposis coli Gly267Term GGA-TGA	CAGAACAAAGCATGAAACCGGCTCACATGATGCTGAGCGGCAG AATGAAGGTCAAGGAGTGGGAGAAATCAACATGGCAACTTCT GGTAATGGTCAGGTAAATAAATTATTTATCATATTT	1485
	AAATATGATAAAATAATTTATTTACCTGACCATTACCAGAAGTT GCCATGTTGATTTCTCCCACTCCTTGACCTTCATTCTGCCGCT CAGCATCATGTGAGCCGGTTTCATGCTTGTCTG	1486
	AAGGAGTGGGAGAAATC	1487
	GATTTCTCCCACTCCTT	1488
Adenomatous polyposis coli Glu443Term GAA-TAA	CTTCAAATAACAAAGCATTATGGTTTATGTTGATTTATTTTCA GTGCCAGCTCCTGTTGAACATCAGATCTGTCCTGCTGTGTGT GTTCTAATGAACTTTCATTTGATGAAGAGCATA	1489
	TATGCTCTTCATCAAATGAAAGTTTCATTAGAACACACACAGCA GGACAGATCTGATGTTCAACAGGAGCTGGCACTGAAAAATAA AATCAACATAAACCATAATGCTTTGTTATTTGAAG	1490
	CTCCTGTTGAACATCAG	1491
	CTGATGTTCAACAGGAG	1492
Adenomatous polyposis coli SER457TER TCA-TAA	CAGTGCCAGCTCCTGTTGAACATCAGATCTGTCCTGCTGTGT GTGTTCTAATGAACTTTTCAATTTGATGAAGAGCATAGACATGC AATGAATGAACTAGGTAAGACAAAAATGTTTTTTAA	1493

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTAAAAACATTTTTGTCTTACCTAGTTCATTTCATTGCATGTCTA TGCTCTTCATCAAATGAAAGTTTCATTAGAACACACACAGCAG GACAGATCTGATGTTCAACAGGAGCTGGCACTG	1494
	GAAACTTTTCATTTGATG	1495
	CATCAAATGAAAGTTTC	1496
Adenomatous polyposis coli Gln473Term CAG-TAG	AGTTGTTTTATTTAGATGATTGTCTTTTCCTCTTGCCCTTTTT AAATTAGGGGGACTACAGGCCATTGCAGAATTATTGCAAGTG GACTGTGAAATGTACGGGCTTACTAATGACCACT	1497
	AGTGGTCATTAGTAAGCCCGTACATTTACAGTCCACTTGCAA TAATTCTGCAATGGCCTGTAGTCCCCCTAATTTAAAAAGGGCA AGAGGAAAAAGACAATCATCTAAAATAAAACAAC	1498
	GGGGACTACAGGCCATT	1499
	AATGGCCTGTAGTCCCC	1500
Adenomatous polyposis coli Tyr486Term TAC-TAG	TTTTAAATTAGGGGGACTACAGGCCATTGCAGAATTATTGCAA GTGGACTGTGAAATGTACGGGCTTACTAATGACCACTACAGTA TTACACTAAGACGATATGCTGGAATGGCTTTGACA	1501
	TGTCAAAGCCATTCCAGCATATCGTCTTAGTGTAATACTGTAG TGGTCATTAGTAAGCCCGTACATTTACAGTCCACTTGCAATA ATTCTGCAATGGCCTGTAGTCCCCCTAATTTAAAA	1502
	GAAATGTACGGGCTTAC	1503
	GTAAGCCCGTACATTC	1504
Adenomatous polyposis coli Arg499Term CGA-TGA	TTGCAAGTGGACTGTGAAATGTATGGGCTTACTAATGACCACT ACAGTATTACACTAAGACGATATGCTGGAATGGCTTTGACAAA CTTGACTTTTTGGAGATGTAGCCAACAAGGTATGTT	1505
	AACATACCTTGTGGCTACATCTCCAAAAGTCAAGTTTGCAA AGCCATTCCAGCATATCGTCTTAGTGTAATACTGTAGTGGTCA TTAGTAAGCCCATACATTTACAGTCCACTTGCAA	1506
	CACTAAGACGATATGCT	1507
	AGCATATCGTCTTAGTG	1508
Adenomatous polyposis coli Tyr500Term TAT-TAG	AGTGGACTGTGAAATGTATGGGCTTACTAATGACCACTACAGT ATTACACTAAGACGATATGCTGGAATGGCTTTGACAACTTGA CTTTTGGAGATGTAGCCAACAAGGTATGTTTTAT	1509
	ATAAAAACATACCTTGTGGCTACATCTCCAAAAGTCAAGTTTG TCAAAGCCATTCCAGCATATCGTCTTAGTGTAATACTGTAGTG GTCATTAGTAAGCCCATACATTTACAGTCCACT	1510
	AGACGATATGCTGGAAT	1511
	ATTCCAGCATATCGTCT	1512
Adenomatous polyposis coli Lys586Term AAA-TAA	GACAAATCCAACCTAATTAGATGACCCATATTCTGTTTCTTA CTAGGAATCAACCCTCAAAAGCGTATTGAGTGCCTTATGGAAT TTGTCAGCACATTGCACTGAGAATAAAGCTGATA	1513
	TATCAGCTTTATTCTCAGTGCAATGTGCTGACAAATTCCATAA GGCACTCAATACGCTTTTGAGGGTTGATTCTAGTAAGAAACA GAATATGGGTCATCTAATTAGAGTTGGAATTTGTC	1514
	CAACCCTCAAAAGCGTA	1515

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TACGCTTTTGAGGGTTG	1516
Adenomatous polyposis coli Leu592Term TTA-TGA	TAGATGACCCATATTCTGTTTCTTACTAGGAATCAACCCTCAAAAGCGTATTGAGTGCCTTATGGAATTTGTCAGCACATTGCACTGAGAATAAAGCTGATATATGTGCTGTAGATGGTGC	1517
	GCACCATCTACAGCACATATATCAGCTTTATTCTCAGTGCAATGTGCTGACAAATCCATAAGGCACTCAATACGCTTTTGAGGGTTGATTCCCTAGTAAGAAACAGAATATGGGTCATCTA	1518
	GAGTGCCTTATGGAATT	1519
	AATTCCATAAGGCACTC	1520
Adenomatous polyposis coli Trp593Term TGG-TAG	ATGACCCATATTCTGTTTCTTACTAGGAATCAACCCTCAAAAGCGTATTGAGTGCCTTATGGAATTTGTCAGCACATTGCACTGAGAATAAAGCTGATATATGTGCTGTAGATGGTGCCT	1521
	AGTGCACCATCTACAGCACATATATCAGCTTTATTCTCAGTGC AATGTGCTGACAAATCCATAAGGCACTCAATACGCTTTTGAGGGTTGATTCCCTAGTAAGAAACAGAATATGGGTCAT	1522
	TGCCTTATGGAATTTGT	1523
	ACAAATTCATAAGGCA	1524
Adenomatous polyposis coli Trp593Term TGG-TGA	TGACCCATATTCTGTTTCTTACTAGGAATCAACCCTCAAAAGCGTATTGAGTGCCTTATGGAATTTGTCAGCACATTGCACTGAGAATAAAGCTGATATATGTGCTGTAGATGGTGCCTT	1525
	AAGTGCACCATCTACAGCACATATATCAGCTTTATTCTCAGTGC AATGTGCTGACAAATCCATAAGGCACTCAATACGCTTTTGAGGGTTGATTCCCTAGTAAGAAACAGAATATGGGTCA	1526
	GCCTTATGGAATTTGTC	1527
	GACAAATTCATAAGGC	1528
Adenomatous polyposis coli Tyr622Term TAC-TAA	TAAAGCTGATATATGTGCTGTAGATGGTGCCTTGCATTTTGTGTTGGCACTCTTACTTACCGGAGCCAGACAAACACTTTAGCCATTATTGAAAGTGGAGGTGGGATATTACGGAATGTG	1529
	CACATTCCGTAATATCCACCTCCACTTTCAATAATGGCTAAA GTGTTTGTCTGGCTCCGTAAGTAAGAGTGCCAACCAAAAATGCAAGTGCACCATCTACAGCACATATATCAGCTTTA	1530
	CTTACTTACCGGAGCCA	1531
	TGGCTCCGTAAGTAAG	1532
Adenomatous polyposis coli Gln625Term CAG-TAG	GATATATGTGCTGTAGATGGTGCCTTGCATTTTGTGTTGGCACTCTTACTTACCGGAGCCAGACAAACACTTTAGCCATTATTGA AAGTGGAGGTGGGATATTACGGAATGTGTCCAGCT	1533
	AGCTGGACACATTCCGTAATATCCACCTCCACTTTCAATAAT GGCTAAAGTGTGTTGTCTGGCTCCGTAAGTAAGAGTGCCAAC CAAAATGCAAGTGCACCATCTACAGCACATATATC	1534
	ACCGGAGCCAGACAAAC	1535
	GTTTGTCTGGCTCCGGT	1536

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Leu629Term TTA-TAA	TAGATGGTGCACCTTGCATTTTTGGTTGGCACTCTTACTTACCG GAGCCAGACAAACACTTTAGCCATTATTGAAAGTGGAGGTGG GATATTACGGAATGTGTCCAGCTTGATAGCTACAAA	1537
	TTTGTAGCTATCAAGCTGGACACATTCCGTAATATCCCACCTC CACTTTCAATAATGGCTAAAGTGTTTGTCTGGCTCCGGTAAGT AAGAGTGCCAAACCAAAATGCAAGTGCACCATCTA	1538
	AAACACTTTAGCCATTA	1539
	TAATGGCTAAAGTGTTT	1540
Adenomatous polyposis coli Glu650Term GAG-TAG	GCCATTATTGAAAGTGGAGGTGGGATATTACGGAATGTGTCC AGCTTGATAGCTACAAATGAGGACCACAGGTATATATAGAGTT TTATATTACTTTTAAAGTACAGAATTCATACTCTCA	1541
	TGAGAGTATGAATTCTGTACTTTAAAAGTAATATAAACTCTAT ATATACCTGTGGTCCTCATTTGTAGCTATCAAGCTGGACACAT TCCGTAATATCCCACCTCCACTTTCAATAATGGC	1542
	CTACAAATGAGGACCAC	1543
	GTGGTCCTCATTTGTAG	1544
Adenomatous polyposis coli Trp699Term TGG-TGA	TGCATGTGGAACCTTTGTGGAATCTCTCAGCAAGAAATCCTAAA GACCAGGAAGCATTATGGGACATGGGGGCAGTTAGCATGCTC AAGAACCTCATTCAATCAAGCACAAAATGATTGCT	1545
	AGCAATCATTTTGTGCTTTGAATGAATGAGGTTCTTGAGCATG CTAACTGCCCCCATGTCCATAATGCTTCCTGGTCTTTAGGAT TTCTTGCTGAGAGATTCCACAAAGTTCCACATGCA	1546
	GCATTATGGGACATGGG	1547
	CCCATGTCCATAATGC	1548
Adenomatous polyposis coli Ser713Term TCA-TGA	AAGACCAGGAAGCATTATGGGACATGGGGGCAGTTAGCATGC TCAAGAACCTCATTCAATCAAGCACAAAATGATTGCTATGGG AAGTGCTGCAGCTTTAAGGAATCTCATGGCAAATAG	1549
	CTATTTGCCATGAGATTCTTAAAGCTGCAGCACTTCCCATAG CAATCATTTTGTGCTTTGAATGAATGAGGTTCTTGAGCATGCT AACTGCCCCCATGTCCATAATGCTTCCTGGTCTT	1550
	CATTCATTCAAAGCACA	1551
	TGTGCTTTGAATGAATG	1552
Adenomatous polyposis coli Ser722Gly AGT-GGT	GGGGCAGTTAGCATGCTCAAGAACCTCATTCAATCAAAGCAC AAAATGATTGCTATGGGAAGTGCTGCAGCTTTAAGGAATCTCA TGGCAAATAGGCCTGCGAAGTACAAGGATGCCAATA	1553
	TATTGGCATCCTTGTACTTCGCAGGCCTATTTGCCATGAGATT CCTTAAAGCTGCAGCACTTCCCATAGCAATCATTTTGTGCTTT GAATGAATGAGGTTCTTGAGCATGCTAACTGCCCC	1554
	CTATGGGAAGTGCTGCA	1555
	TGCAGCACTTCCCATAG	1556

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Leu764Term TTA-TAA	TCTCCTGGCTCAGCTTGCCATCTCTTCATGTTAGGAAACAAAA AGCCCTAGAAGCAGAATTAGATGCTCAGCACTTATCAGAACT TTTGACAATATAGACAATTTAAGTCCCAAGGCATC	1557
	GATGCCTTGGGACTTAAATTGTCTATATTGTCAAAGTTTCTGA TAAGTGCTGAGCATCTAATTCTGCTTCTAGGGCTTTTTGTTTC CTAACATGAAGAGATGGCAAGCTGAGCCAGGAGA	1558
	AGCAGAATTAGATGCTC	1559
	GAGCATCTAATTCTGCT	1560
Adenomatous polyposis coli Ser784Thr TCT-ACT	TTAGATGCTCAGCACTTATCAGAACTTTTGACAATATAGACAA TTTAAGTCCCAAGGCATCTCATCGTAGTAAGCAGAGACACAG CAAGTCTCTATGGTGATTATGTTTTTGACACCATC	1561
	GATGGTGTCAAAAACATAATCACCATAGAGACTTGCTGTGTCT CTGCTTACTACGATGAGATGCCTTGGGACTTAAATTGTCTATA TTGTCAAAAGTTTCTGATAAGTGCTGAGCATCTAA	1562
	CCAAGGCATCTCATCGT	1563
	ACGATGAGATGCCTTGG	1564
Adenomatous polyposis coli Arg805Term CGA-TGA	CTCATCGTAGTAAGCAGAGACACAGCAAGTCTCTATGGTGATT ATGTTTTTGACACCAATCGACATGATGATAATAGGTCAGACAT TTTAATACTGGCAGATGACTGTCTTTTACCATAT	1565
	ATATGGTGAAAGGACAGTCATGTGCCAGTATTAAAATGTCTGA CCTATTATCATCATGTGCGATTGGTGTCAAAAACATAATCACCAT AGAGACTTGCTGTGTCTCTGCTTACTACGATGAG	1566
	ACACCAATCGACATGAT	1567
	ATCATGTGCGATTGGTGT	1568
Adenomatous polyposis coli Gln879Term CAG-TAG	GGTCTAGGCAACTACCATCCAGCAACAGAAAATCCAGGAACT TCTTCAAAGCGAGGTTTGAGATCTCCACCACTGCAGCCCAG ATTGCCAAAGTCATGGAAGAAGTGTCAGCCATTCTATA	1569
	TATGAATGGCTGACACTTCTTCCATGACTTTGGCAATCTGGGC TGCAGTGGTGGAGATCTGCAAACCTCGCTTTGAAGAAGTTCC TGGATTTTCTGTTGCTGGATGGTAGTTGCCTAGACC	1570
	GAGGTTTGAGATCTCC	1571
	GGAGATCTGCAAACCTC	1572
Adenomatous polyposis coli Ser932Term TCA-TAA	TACATTGTGTGACAGATGAGAGAAATGCACCTAGAAGAAGCTC TGCTGCCCATACACATTCAAACACTTACAATTTCACTAAGTCG GAAAATTCAAATAGGACATGTTCTATGCCTTATGC	1573
	GCATAAGGCATAGAACATGTCCTATTTGAATTTCCGACTTAG TGAAATTGTAAGTGTTTGAATGTGTATGGGCAGCAGAGCTTCT TCTAAGTGCATTTCTCTCATCTGTACACAATGTA	1574
	TACACATTCAAACACTT	1575
	AAGTGTTTGAATGTGTA	1576
Adenomatous polyposis coli Ser932Term TCA-TGA	TACATTGTGTGACAGATGAGAGAAATGCACCTAGAAGAAGCTC TGCTGCCCATACACATTCAAACACTTACAATTTCACTAAGTCG GAAAATTCAAATAGGACATGTTCTATGCCTTATGC	1577